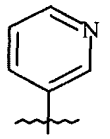
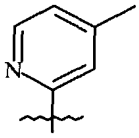
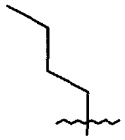
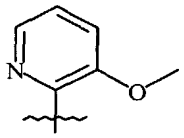
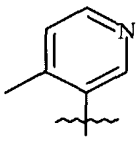
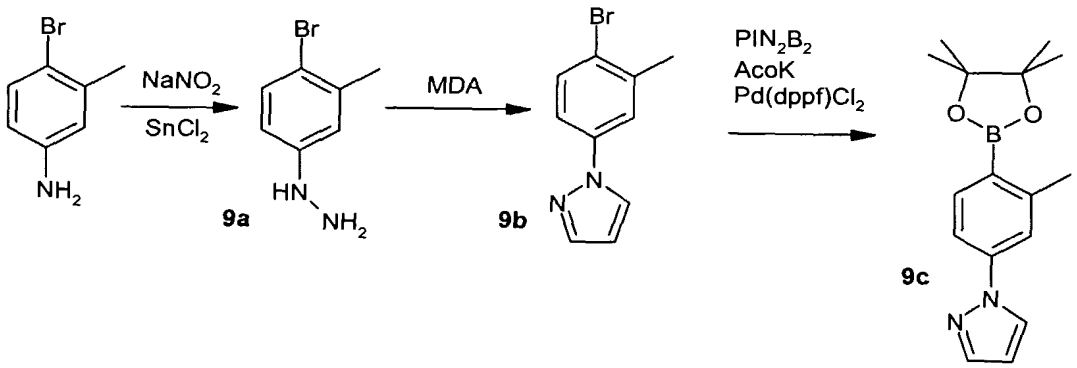
| Cmpd | $R_2$ | MW | MS | $t_R$* |
|---|---|---|---|---|
| 8-8 |  | 396.452 | 396 | 4.940 |
| 8-9 |  | 410.479 | 410 | 5.640 |
| 8-10 |  | 375.474 | 375 | 6.260 |
| 8-11 |  | 426.478 | 426 | 5.850 |
| 8-12 |  | 410.479 | 410 | 4.700 |

* All HPLC determinations employed Analytical Method 2.

## EXAMPLE 9

SYNTHESIS OF REAGENT 2-METHYL-4-(PYRAZOL-1-YL)PHENYLBORONIC ACID PINACOL ESTER






SPRUCE – EXHIBIT 2008
Neurocrine Biosciences, Inc. v. Spruce Biosciences, Inc. PGR2026-00059
3506

Step 9A:

4-Bromo-3-methylaniline (10.2 g) was suspended in 6N HCl (85 mL) and cooled to 0 °C. A solution of sodium nitrite (4 g in 40 mL $H_2O$) was added over 10 min. The reaction was stirred for 15 min at 0 °C followed by the addition of stannous chloride dihydrate (36 g in 25 mL 12N HCl.) The reaction was stirred for 2 hr at 0 °C. The reaction was filtered and the filter cake washed with cold $H_2O$ to afford 4-bromo-3-methylphenylhydrazine hydrochloride (Cmpd **9a**, 20 g) as a tan solid.

Step 9B:

The compound resulting from Step 9A (20 g) was suspended in 50 mL ethanol. Malondialdehyde bis-dimethylacetal (11.0 mL, 67 mmol) was added and the reaction was heated to 85 °C for 2 hr. The reaction mixture was neutralized with sodium bicarbonate and extracted by washing with DCM. The combined organic layers were dried over magnesium sulfate and concentrated. The residue was taken up in ethyl acetate and the mixture filtered through a pad of Celite®. The filtrate was evaporated, and the oily residue was purified by column chromatography (1:1 ethyl acetate: hexanes) to afford 1-(4-bromo-3-methylphenyl)pyrazole (Cmpd **9b**, 9.6 g, 73%) as an amber oil.

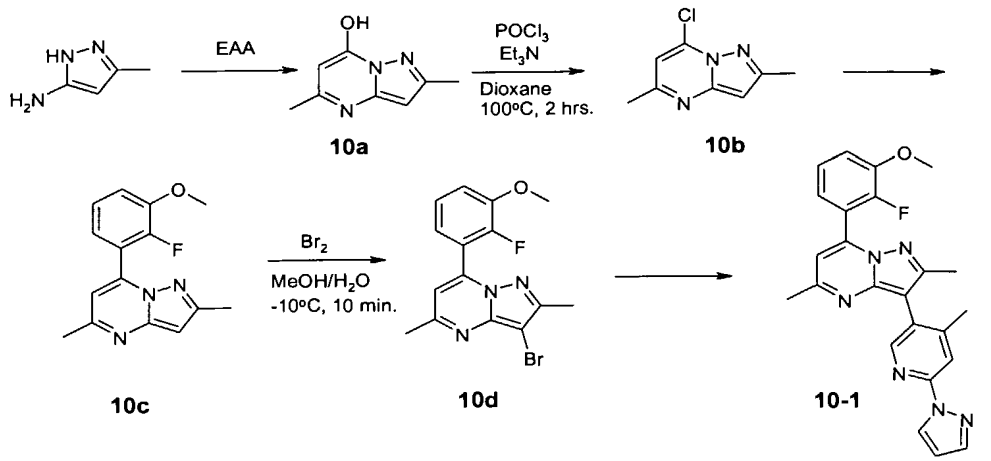
Step 9C:

To a solution of Cmpd **9b** (2.0 g in 15 mL dioxane) was added bis(pinacolato)diboron (2.4 g), potassium acetate (2.4 g) and 1,1'-bis(diphenylphosphino) ferrocene dichloropalladium (II) (500 mg.) The reaction was heated to 85 °C for 12 hr. The reaction mixture was filtered through a pad of Celite® and the filter cake washed with ethyl acetate. The filtrate was concentrated to a brown liquid which was purified by column chromatography (20% ethyl acetate:hexanes) to afford 2-methyl-4-(pyrazol-1-yl)phenylboronic acid pinacol ester (Cmpd **9c**, 1.8 g, 75%) as a yellow oil; LC/MS: [M+H] = 285.0.

Also prepared by the methods above were 2-chloro-4-(pyrazol-1-yl)phenylboronic acid pinacol ester (**9d**) and 2-methyl-3-(pyrazol-1-yl)phenylboronic acid pinacol ester (**9e**).

## EXAMPLE 10

7-(2-FLUORO-3-METHOXY-PHENYL)-2,5-DIMETHYL-3-(4-METHYL-6-PYRAZOL-1-YL-PYRIDIN-3-YL)-PYRAZOLO[1,5-A]PYRIMIDINE




Step 10A:

A solution of 3-amino-5-methylpyrazole (20.0 g, 206 mmol), ethyl acetoacetate (32.0 g, 247 mmol), acetic acid (6 mL), and dioxane (150 mL) was refluxed for 16 hr. A white solid precipitated, which was collected by filtration. The filter cake was washed with ether to provide **10a** (29.0 g, 86 %) as a white solid.

Step 10B:

To a suspension of compound **10a** (5.0 g, 31 mmol) in 1,4-dioxane (30 mL) was added triethylamine (8.50 mL, 62 mmol) and phosphorous oxychloride (7.4 mL, 77 mmol). The reaction was heated under nitrogen at 100°C for 2 hr. The reaction mixture was cooled in an ice bath, then treated successively with water and aqueous sodium bicarbonate solution (final pH 8). Dichloromethane was added and the mixture was washed 3x with water. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to a dark brown oil. The crude product was purified by silica gel chromatography using 30% ethyl acetate in hexanes as eluent, providing **10b** (3.8 g, 70%) as a white solid.

Step 10C:

To a mixture of 80 mL dioxane and 8 mL water were added compound **10b** (3.3 g, 18 mmol, 1 eq), 2-fluoro-3-methoxyphenylboronic acid (4.3 g, 26 mmol, 1.4 eq), potassium carbonate (5.0 g, 36 mmol, 2 eq), and

tetrakis(triphenylphosphine)palladium(0) (1.5 g, 1.3 mmol, 0.07 eq). The mixture was stirred and heated at 100 °C for 16 hr, then was allowed to cool and water (75 mL) was added. The mixture was extracted with ethyl acetate, then the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 4:1 hexane/ethyl acetate to provide Cmpd **10c** (3.78 g, 76 %) as white solid.

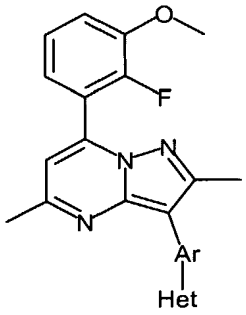
Step 10D:

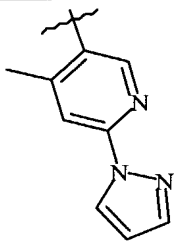
Bromine (1.77 g, 11 mmol) was added to a solution of **10c** (3.0 g, 11 mmol) in methanol (30 mL) at –10 °C. After 10 min, the mixture was filtered to collect the precipitate that had formed. The filter cake was washed with cold methanol, and was then dried under vacuum to yield **10d** (3.15 g, 83 %) as a yellow solid .

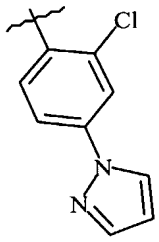
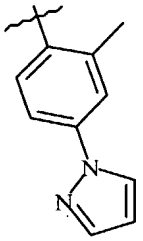
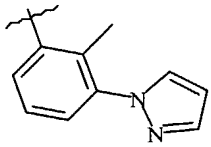
Step 10E:

Suzuki reaction of Cmpd **10d** (460 mg, 1.3 mmol) according to the procedure of Step 10C above, using Cmpd **12-1** in place of 2-fluoro-3-methoxyphenylboronic acid, yielded Cmpd **10-1** (15 mg, solid) following purification by prep HPLC/MS and silica gel chromatography (4:1 hexane/ethyl acetate eluent).

Depending on the boronate ester or acid employed in the final Suzuki reaction, the compounds listed in the following table were synthesized and purified by preparative LC-MS:



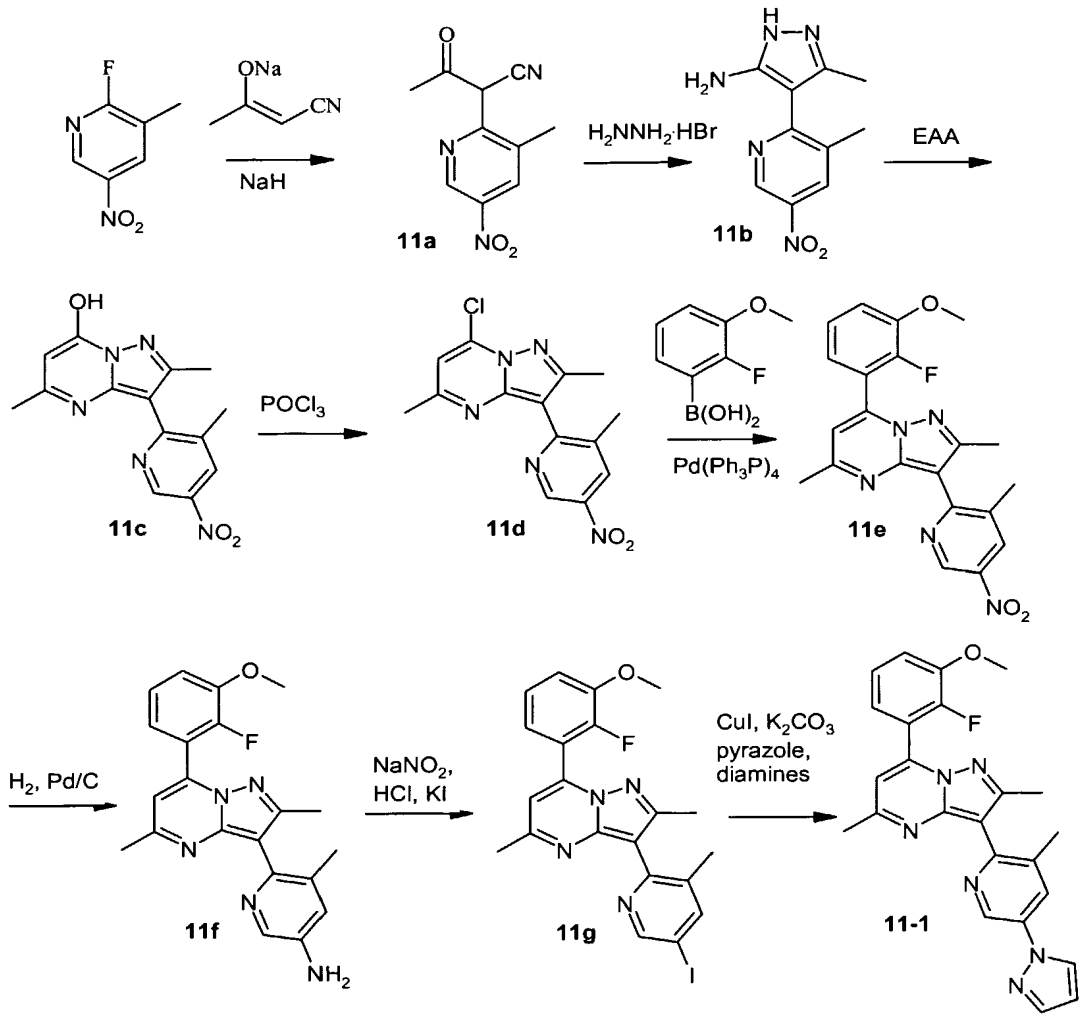

| Cmpd | AR-HET | MW | MS | $t_R$* |
|---|---|---|---|---|
| **10-1** |  | 428.469 | 429 | 8.110 |

| | | | | |
|---|---|---|---|---|
| **10-2** |  | 447.899 | 447 | 6.390 |
| **10-3** |  | 427.481 | 427 | 6.330 |
| **10-4** |  | 427.481 | 427 | 7.670 |

* All HPLC determinations employed Analytical Method 2.

## EXAMPLE 11

7-(2-FLUORO-3-METHOXY-PHENYL)-2,5-DIMETHYL-3-(3-METHYL-5-PYRAZOL-1-YL-PYRIDIN-2-YL)-PYRAZOLO[1,5-A]PYRIMIDINE




Step 11A:

Sodium hydride (1.54 g of 60 % dispersion in oil, 38.5 mmol, 2 eq) was added to a solution of cyanoacetone sodium salt (2.5 g, 23 mmol, 1.2 eq) in DMF (40 mL) at RT. The mixture was stirred for 15 min, then a solution of 2-fluoro-3-methyl-5-nitropyridine (3.0 g, 19.2 mmol, 1.0 eq) in 10 mL DMF was added dropwise. The reaction mixture was stirred at RT for 6 hr. The reaction was quenched with 5 g ice, followed by 150 mL water and 10 mL acetic acid. The mixture was extracted with ethyl acetate, then the combined organic extracts were dried over sodium sulfate, filtered,

and concentrated. The residue was purified by silica gel chromatography using 30% ethyl acetate in hexanes as eluent, providing **11a** (1.85 g, 44 % yield) as an orange oil.

Step 11B:

A mixture of **11a** (1.8 g, 8.2 mmol, 1.0 eq), hydrazine monohydrobromide (1.0 g, 8.8 mmol, 1.1 eq), ethanol (30 mL) and water (3 mL) was heated at reflux for 17 hr. The solvent was evaporated, and the residue was purified directly by silica gel chromatography using 1:1 hexanes/ethyl acetate as eluent, obtaining **11b** (1.8 g, 94 % yield) as a yellow foam.

Step 11C:

A mixture of **11b** (1.8 g, 7.7 mmol, 1.0 eq), ethanol (15 mL), acetic acid (15 mL), and ethyl acetoacetate (1.6 g, 12.4 mmol, 1.6 eq) was heated in a sealed tube at 105 °C for 19 hr. The solvent was evaporated, and the residue was deposited on a fritted glass filter, rinsing with ether, to provide **11c** (1.0 g, 43 % yield) as a yellow solid.

Step 11D:

A mixture of **11c** (800 mg, 2.7 mmol, 1.0 eq), phosphorous oxychloride (900 mg, 5.9 mmol, 2.2 eq), and acetonitrile (15 mL) was refluxed for 3 hr. The reaction was poured onto ice, then the mixture was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with aqueous sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to provide **11d** (640 mg, 76 %) as a yellow solid.

Step 11E:

A suspension of **11d** (640 mg, 2.0 mmol,1 eq), 2-fluoro-3-methoxyphenylboronic acid (480 mg, 3.8 mmol, 1.4 eq), potassium carbonate (555 mg, 4.0 mmol, 2.0 eq), tetrakis(triphenylphosphine)palladium(0) (230 mg, 0.2 mmol, 0.1 eq) in 20 mL dioxane and 2 mL water was stirred and heated at 100 °C for 16 hr. Water (50 mL) was added and the mixture was extracted with ethyl acetate (50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was triturated with methanol to obtain **11e** (300 mg, 37 %) as a yellow solid.

Step 11F:

10 % Pd/C (100 mg) was added to a nitrogen-sparged solution of **11e** (300 mg, 0.74 mmol, 1.0 eq) in 20 mL ethanol and 10 mL THF. The mixture was shaken in a Parr shaker under 40 psi hydrogen gas at RT for 6 hr. The mixture was purged with nitrogen and filtered. The filtrate was concentrated to provide **11f** (260 mg, 94% yield) as a yellow oil.

Step 11G:

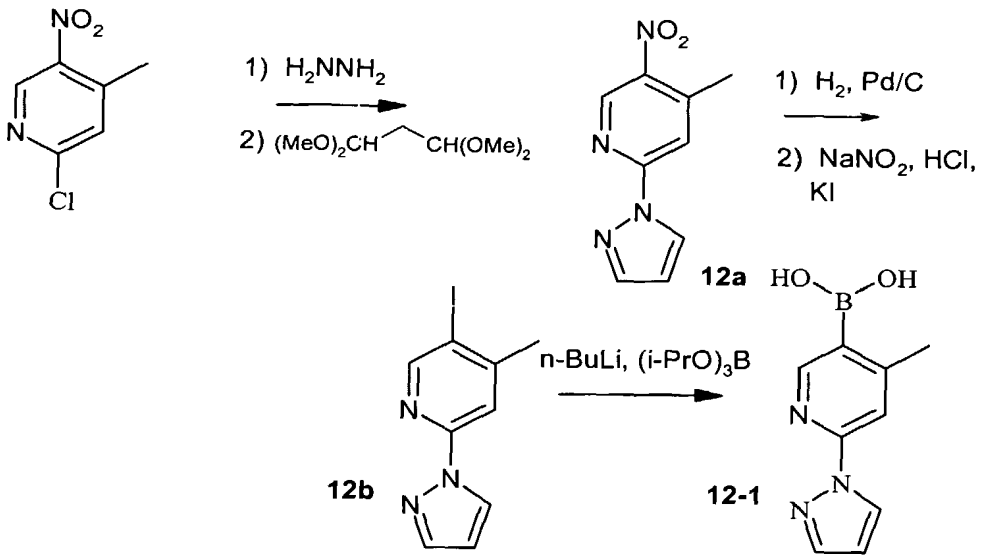
A solution of sodium nitrite (60 mg, 0.87 mmol, 1.3 eq) in water (10 mL) was added dropwise to an ice-cold solution of **11f** (260 mg, 0.69 mmol, 1.0 eq) in 4N hydrochloric acid (5 mL). The mixture was stirred at 0 °C for 1 hr, followed by addition of 10 mL of half-saturated aqueous potassium iodide. The mixture was stirred at RT for 16 hr, then 50 mL saturated aqueous sodium bicarbonate solution was added and the mixture was extracted 2x 50 mL ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, concentrated and the residue purified by silica gel chromatography using 4:1 hexanes/ethyl acetate as eluent, providing **11g** (170 mg, 51 % yield) as a yellow solid.

Step 11H:

To a solution of **11g** (170 mg, 0.35 mmol, 1.0 eq) in dioxane (6 mL) were added potassium carbonate (200 mg, 1.45 mmol, 4.1 eq), pyrazole (60 mg, 0.89 mmol, 2.5 eq), copper(I) iodide (60 mg, 0.32 mmol, 0.9 eq), trans-1,2-diaminocyclohexane (36 mg, 0.32 mmol, 0.9 eq), and N,N'-dimethylethylenediamine (28 mg, 0.32 mmol, 0.9 eq). The mixture was stirred and heated in a sealed tube at 100 °C for 19 hr. The reaction mixture was filtered through a Celite® pad, concentrated, and purified by prep HPLC/MS to obtain Cmpd **11-1** (70 mg, 37 % yield) as a TFA salt; MW: 428.47; LC/MS: 429 $[MH]^+$; $t_R$: 5.390, Anal. Meth. 2.

## EXAMPLE 12

4-METHYL-2-PYRAZOL-1-YL-5-PYRIDYLBORONIC ACID




Step 12A:

2-Chloro-4-methyl-5-nitropyridine (5.0 g, 29 mmol, 1.0 eq) was dissolved in 50 mL hydrazine solution (1M solution in THF) and the mixture was stirred and heated in a sealed tube at 80 °C for 22 hr. The cooled reaction mixture was filtered, and the solid obtained was washed with ether to provide 5.7 g of a greenish brown solid.

A mixture of this solid (5.7 g, 24 mmol, 1.0 eq), malonaldehyde bis(dimethylacetal) (5.9 g, 31 mmol, 1.3 eq), and acetic acid (50 mL) was stirred and heated in a sealed tube at 80 °C for 5 hr. The solvent was evaporated, then aqueous sodium bicarbonate solution (200 mL) was added and the mixture was extracted with 2 x 200 mL ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was recrystallized from ethanol to obtain **12a** (2.6 g, 53 % yield) as a yellow solid.

Step 12B:

A mixture of **12a** (2.6 g, 13 mmol) and 10 % Pd/C (200 mg) in 30 mL of 1:1 THF/methanol was shaken in a Parr apparatus under 40 psi hydrogen at RT for 2 hr. The reaction mixture was filtered through a Celite® pad and the filtrate concentrated to a light green oil. The oil was resuspended in 10 mL of 3N hydrobromic acid, cooled

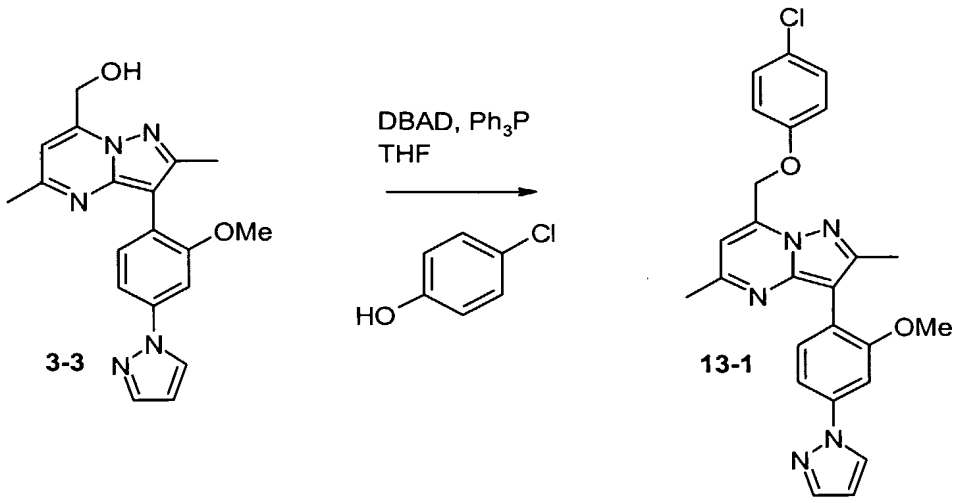
to 0 °C, then treated dropwise with a solution of sodium nitrite (835 mg, 12 mmol, 1.1 eq) in 2 mL water. The mixture was stirred at 0 °C for 1 hr, then 2 mL of half-saturated potassium iodide was added and the mixture was stirred at RT for 22 hr. Saturated aqueous sodium bicarbonate solution was added, then the mixture was extracted with 2x 100 mL ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using 4:1 hexanes/ethyl acetate as eluent, to provide **12b** (1.23 g, 33 %) as a yellow solid.

Step 12C:

n-Butyllithium (1.8 mL of a 2.0 M solution in pentane, 3.6 mmol) was added dropwise to a solution of Cmpd **12b** (600 mg, 2.1 mmol) and triisopropylborate (900 mg, 4.8 mmol) in 5 mL THF at –78 °C. The mixture was allowed to warm to RT over 1 hr, then the mixture was cooled to –78 °C and treated with additional triisopropylborate (400 mg, 2.1 mmol), followed by additional n-butyllithium (0.5 mL of a 2.0 M solution in pentane, 1.0 mmol). The mixture again was allowed to warm to RT over 1 hr, then 0.8 mL of 1N hydrochloric acid was added and the mixture was stirred for 1 hr. The mixture was filtered, rinsing the solid with methanol and ethyl acetate, then the filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 1:1 hexanes/ethyl acetate to provide Cmpd **12-1** (220 mg, 52 % yield) as a red solid.

## EXAMPLE 13

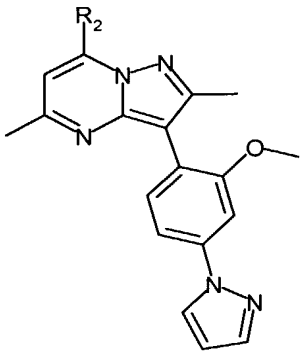
7-(4-CHLORO-PHENOXYMETHYL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

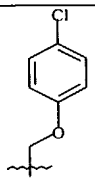
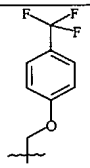
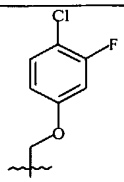
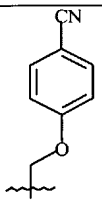
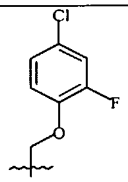
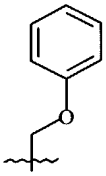



Step 13A:

To a solution of Cmpd **3-3** (25 mg, 0.072 mmol, 1 eq) in THF (1.5 mL) were added di-*tert*-butylazodicarboxylate (30 mg, 0.11 mmol, 1.5 eq), triphenylphosphine (30 mg, 0.11 mmol, 1.5 eq) and 4-chlorophenol (30 mg, 0.023 mmol, 3.3 eq). The mixture was stirred at RT for 17 hr, then the solvent was evaporated and the residue was purified by silica gel chromatography, eluting with hexanes/ethyl acetate to provide Cmpd **13-1** (8 mg) as a solid.

Depending on the phenol employed, the compounds listed in the following table were synthesized and purified by preparative LC-MS:

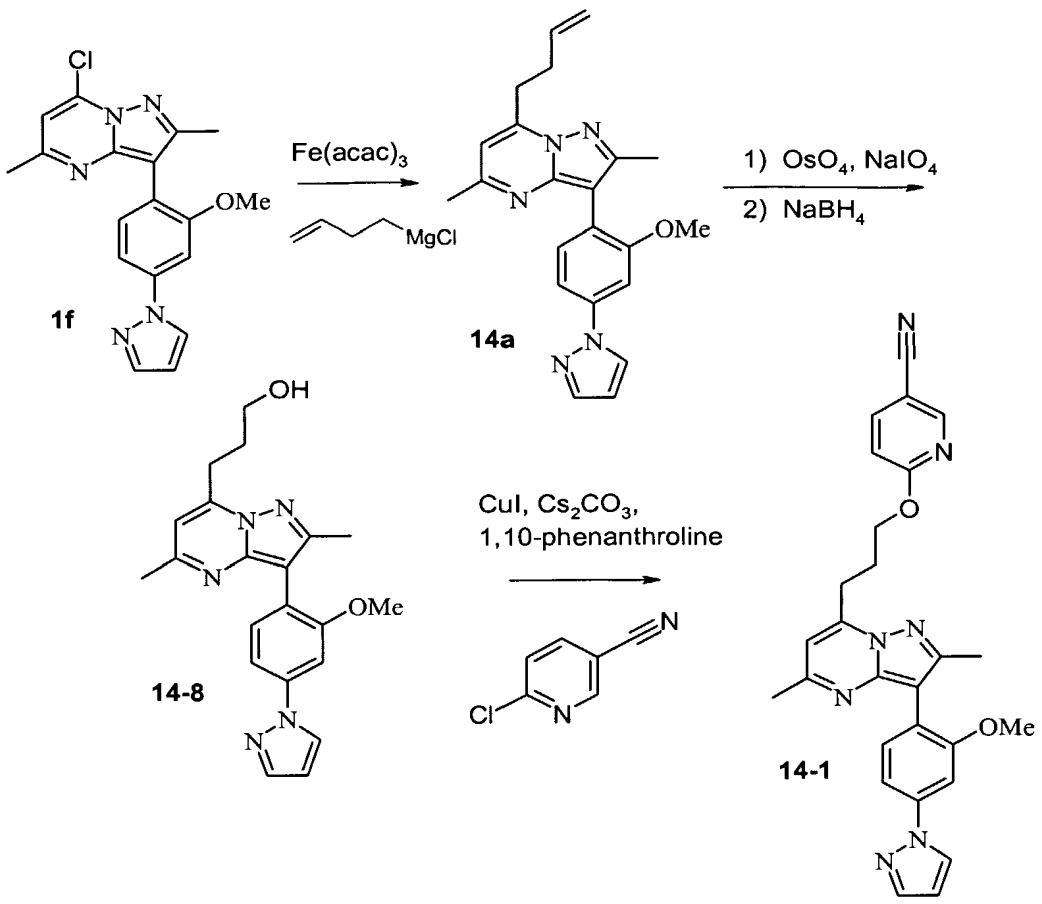


| Cmpd | $R_2$ | MW | MS | $t_R$* |
|---|---|---|---|---|
| 13-1 |  | 459.935 | 460 | 9.090 |
| 13-2 |  | 493.487 | 494 | 7.690 |
| 13-3 |  | 477.925 | 478 | 9.210 |
| 13-4 |  | 450.5 | 451 | 7.850 |
| 13-5 |  | 477.925 | 478 | 9.170 |
| 13-6 |  | 425.49 | 426 | 8.420 |

* All HPLC determinations employed Analytical Method 2.

## EXAMPLE 14

6-{3-[3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDIN-7-YL]-PROPOXY}-NICOTINONITRILE




Step 14A:

To a solution of Cmpd **1f** (1.06 g, 3.0 mmol) and iron(III)acetylacetonate (353 mg, 1.0 mmol) in 10 mL anhydrous THF/NMP (7:1) was added slowly 3-butenylmagnesium chloride (9.0 mL of a 0.5 M solution in THF, 4.5 mmol). The reaction mixture was stirred at RT for 1 hr, then more iron(III)acetylacetonate (1.0 g, 2.8 mmol) and Grignard reagent (6.0 mL, 3.0 mmol) were added. The reaction mixture was stirred for 2 hr, then water was added. The mixture was extracted with ethyl acetate, then the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent to provide **14a** (538 mg, 48 % yield).

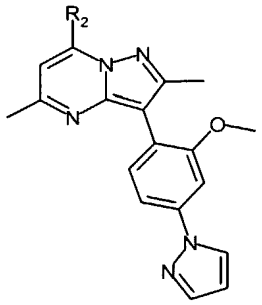
Step 14B:

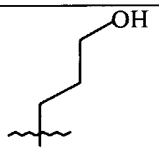
To a solution of **14a** (380 mg, 1.02 mmol) in 10 mL THF/water (4:1) was added osmium tetroxide (26 mg, 0.10 mmol) followed by sodium periodate (642 mg, 3.0 mmol) at RT. The mixture was stirred at RT for 1 hr, then ethyl acetate and water were added. The organic layer was dried over sodium sulfate, filtered, and evaporated to provide the crude aldehyde, which was dissolved in methanol (20 mL). Sodium borohydride (152 mg, 4.0 mmol) was added portionwise. After stirring at room temperature for 20 min, the reaction mixture was concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/ethyl acetate to provide Cmpd **14-1** (230 mg, 60 % yield).

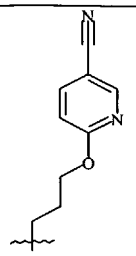
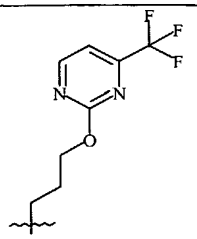
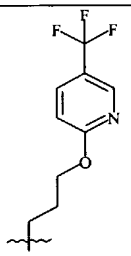
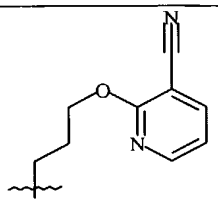
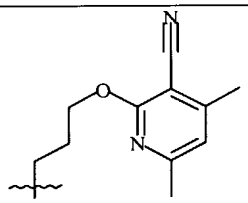
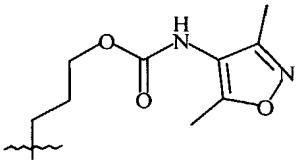
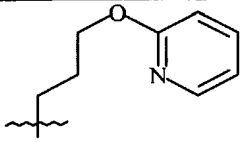
Step 14C:

A mixture of **14-1** (30 mg, 0.08 mmol, 1 eq), copper(I) iodide (15 mg, 0.08 mmol, 1 eq), cesium carbonate (52 mg, 0.16 mmol, 2 eq), and 1,10-phenanthroline (14 mg, 0.08 mmol, 1 eq) was heated in 1 mL of toluene in a sealed vial at 110 °C for 17 hr. The cooled mixture was filtered through Celite®, then concentrated. The residue was purified by silica gel chromatography using hexane/ethyl acetate as eluent to provide **14-2** (5 mg) as a solid.

Depending on the aryl halide used in the method of Step 14C, the compounds listed in the following table in additional to Cmpd **14-1** were synthesized and purified by preparative LC-MS.



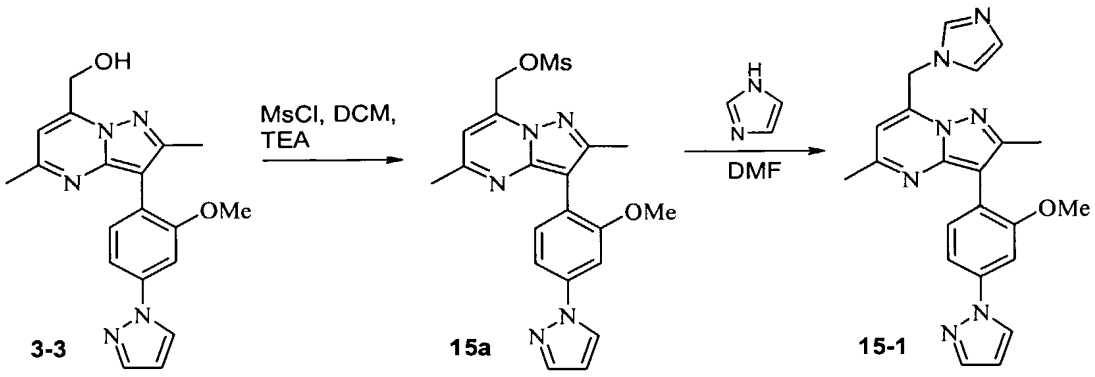

| Cmpd | $R_2$ | MW | MS | $t_R$* |
|---|---|---|---|---|
| **14-1** |  | 377.446 | 377 | 5.170 |

| Cmpd | $R_2$ | MW | MS | $t_R$* |
|---|---|---|---|---|
| 14-2 |  | 479.542 | 479 | 7.570 |
| 14-3 |  | 523.517 | 523 | 8.020 |
| 14-4 |  | 522.529 | 522 | 6.620 |
| 14-5 |  | 479.542 | 479 | 7.350 |
| 14-6 |  | 507.595 | 507 | 8.320 |
| 14-7 |  | 515.571 | 515 | 6.510 |
| 14-8 |  | 454.531 | 454 | 6.690 |

* All HPLC determinations employed Analytical Method 2.

## EXAMPLE 15

7-IMIDAZOL-1-YLMETHYL-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



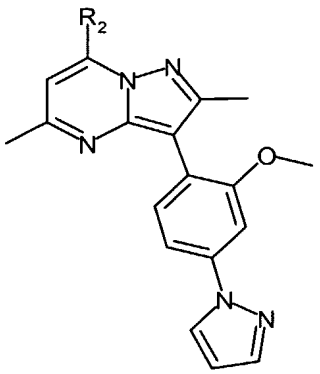

Step15A:

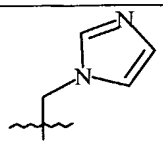
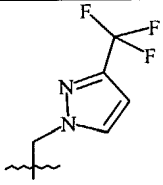
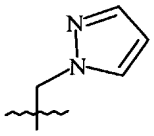
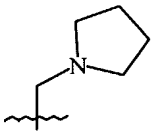
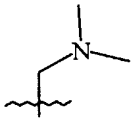
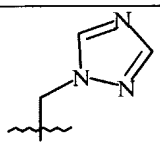
A solution of methanesulfonyl chloride (100 mg, 0.86 mmol, 1.5 eq) in DCM (0.5 mL) was added dropwise to a 0 °C solution of Cmpd **3-3** (200 mg, 0.57 mmol, 1 eq) in 5 mL DCM. The mixture was allowed to warm to RT over 1 hr, then saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with 2 x 20 mL DCM. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to obtain **15a** (180 mg, 49 % yield) as a yellow foam.

Step 15B:

Potassium carbonate (20 mg, 0.14 mmol, 2.6 eq) and imidazole (20 mg, 0.30 mmol, 5.5 eq) were added to a solution of **15a** (23 mg, 0.054 mmol, 1 eq) in DMF (1 mL). The reaction mixture was stirred at RT for 16 hr, then methanol (1 mL) was added and the reaction mixture was purified directly by preparative HPLC/MS, providing **15-1** (10 mg) as a TFA salt.

Depending on the nucleophilic heterocycle or amine employed, the compounds listed in the following table were synthesized and purified by preparative LC-MS:

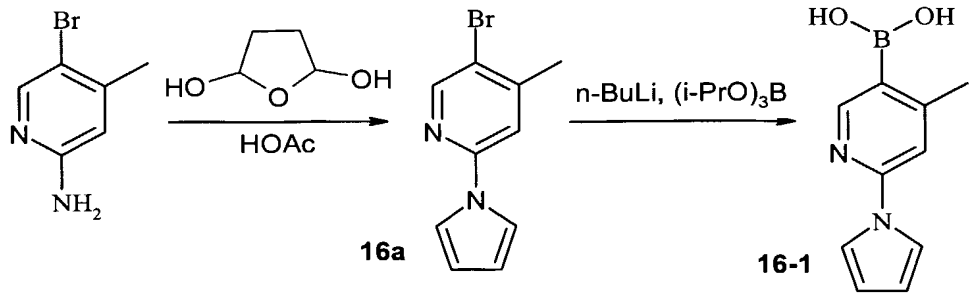


| Cmpd | $R_2$ | MW | MS | $t_R$* |
|---|---|---|---|---|
| 15-1 |  | 399.456 | 400 | 4.190 |
| 15-2 |  | 467.453 | 468 | 6.320 |
| 15-3 |  | 399.456 | 400 | 5.520 |
| 15-4 |  | 402.499 | 403 | 4.110 |
| 15-5 |  | 376.462 | 377 | 3.880 |
| 15-6 |  | 400.444 | 401 | 5.330 |

* All HPLC determinations employed Analytical Method 2.

## EXAMPLE 16

### 4-METHYL-2-PYRROL-1-YL-5-PYRIDYLBORONIC ACID




Step 16A:

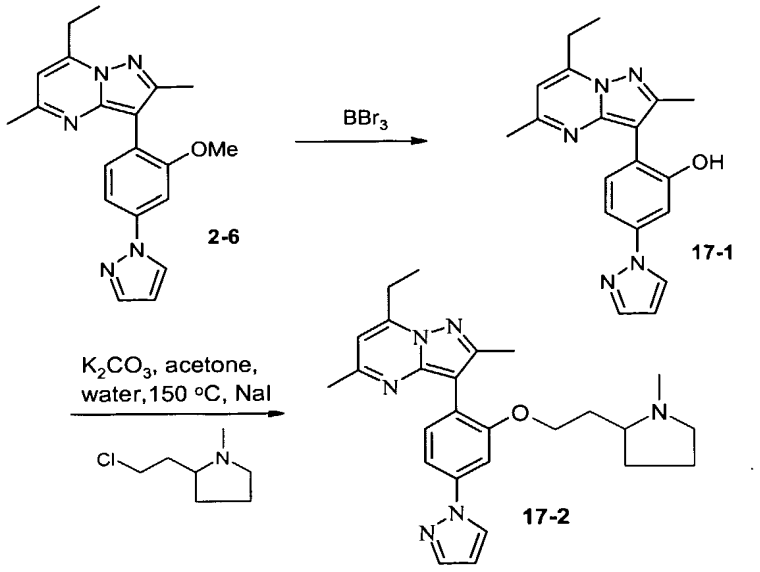
A solution of 2-amino-5-bromo-4-methylpyridine (1 g, 5.4 mmol) and 2,5-dihydroxytetrahydrofuran (2.8 g, 27 mmol) in acetic acid (10 mL) was heated at 90 °C in a sealed tube for 2 hr. The reaction mixture was concentrated and the residue was purified by silica gel chromatography using 4:1 hexanes/ethyl acetate, providing **16a** (900 mg, 71 % yield) as a light yellow oil.

Step 16B:

n-Butyllithium (3.6 mL of a 2.0 M solution in pentane, 7.2 mmol) was added dropwise to a solution of Cmpd **16a** (860 mg, 3.6 mmol) and triisopropylborate (1.4 g, 7.3 mmol) in 6 mL THF at –78 °C. The mixture was allowed to warm to RT over 1 hr, then 0.5 mL of 4N hydrochloric acid was added and the mixture was stirred for 10 min. The mixture was extracted 2x 25 mL DCM, then the organic layer was dried over sodium sulfate, filtered, and concentrated to provide **16-1** (250 mg) as a yellow oil. The aqueous layer was concentrated, then the solid residue was washed with ethanol. The combined ethanol filtrates were concentrated to provide additional **16-1** (500 mg) as a yellow oil.

## EXAMPLE 17

7-ETHYL-2,5-DIMETHYL-3-{2-[2-(1-METHYL-PYRROLIDIN-2-YL)-ETHOXY]-4-PYRAZOL-1-YL-PHENYL}-PYRAZOLO[1,5-A]PYRIMIDINE




Step 17A:

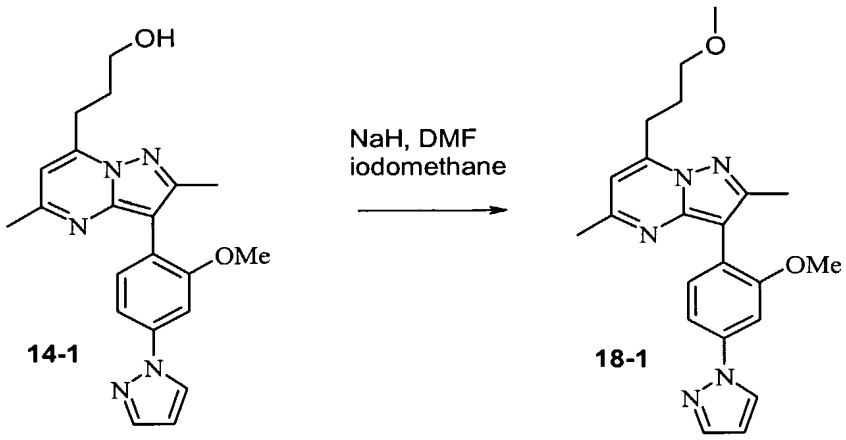
To a solution of Cmpd **2-6** (350 mg) in chloroform (5 mL) was added $BBr_3$ (1.0 M in DCM, 5 mL.) The mixture was stirred overnight at room temperature and quenched with water. The mixture was extracted with chloroform (2x 10 mL), then the combined organic extracts were dried over sodium sulfate, filtered, and concentrated to provide Cmpd **17-1** (280 mg) as an oil. An aliquot (10 mg) was purified by prep HPLC/MS to provide purified Cmpd **17-1** (2.9 mg.)

Step 17B:

A mixture of Cmpd **17-1** (45 mg, 0.14 mmol, 1 eq), potassium carbonate (56 mg, 0.41 mmol, 3 eq), sodium iodide (20 mg, 0.13 mmol, 1 eq), 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (39 mg, 0.21 mmol, 1.5 eq), acetone (1 mL) and water (1 mL) was heated in a sealed tube in a microwave reactor at 150 °C for 25 min. The acetone was evaporated, then the residue was diluted with methanol, filtered, and subjected directly to preparative HPLC/MS purification, yielding Cmpd **17-2** (14 mg, 20%) as a TFA salt; MW: 444.58; LC/MS: 444 $[MH]^+$; $t_R$: 6.010, Anal. Meth. 2.

## EXAMPLE 18

7-(3-METHOXY-PROPYL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

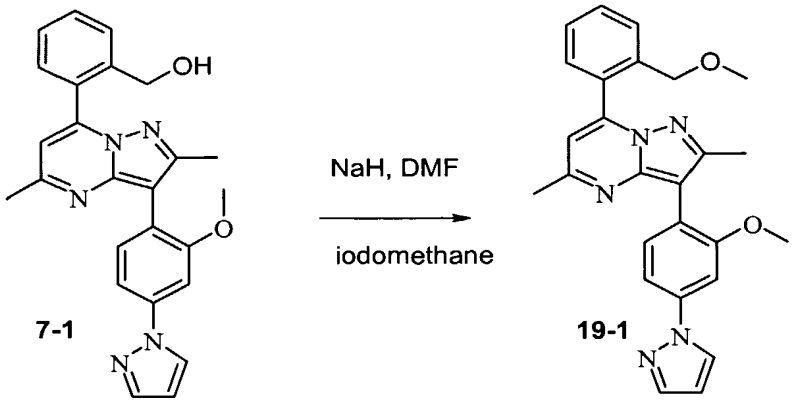



Step 18A:

To a solution of **14-1** (30 mg) in dry DMF was added NaH (10 mg, 60% dispersion). After stirring at RT for 10 min, methyliodide (0.015 mL) was added. The mixture was stirred for 1 hr, then methanol (1 mL) was added and the mixture was subjected directly to prep HPLC/MS purification, providing Cmpd **18-1** (12 mg) as a TFA salt; MW: 391.47 LC/MS: 391 $[MH]^+$; $t_R$: 7.050, Anal. Meth. 2.

## EXAMPLE 19

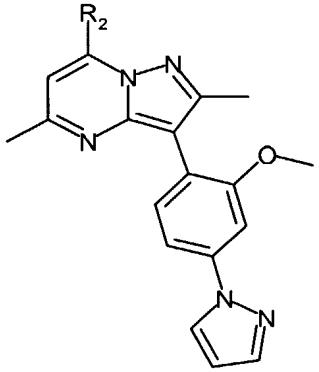
2-[7-(2-METHOXYMETHYL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDIN-3-YL]-5-PYRAZOL-1-YL-PHENOL

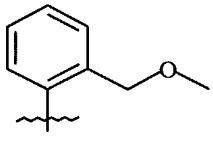


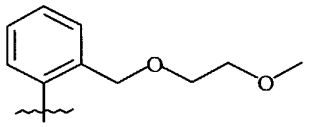
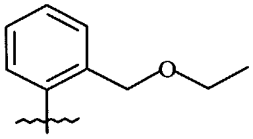

Step 19A:

The procedure of Example 18 was followed using Cmpd **7-1** as starting material

Depending on the alkyl halide employed, the compounds listed in the following table were synthesized and purified by preparative LC-MS.

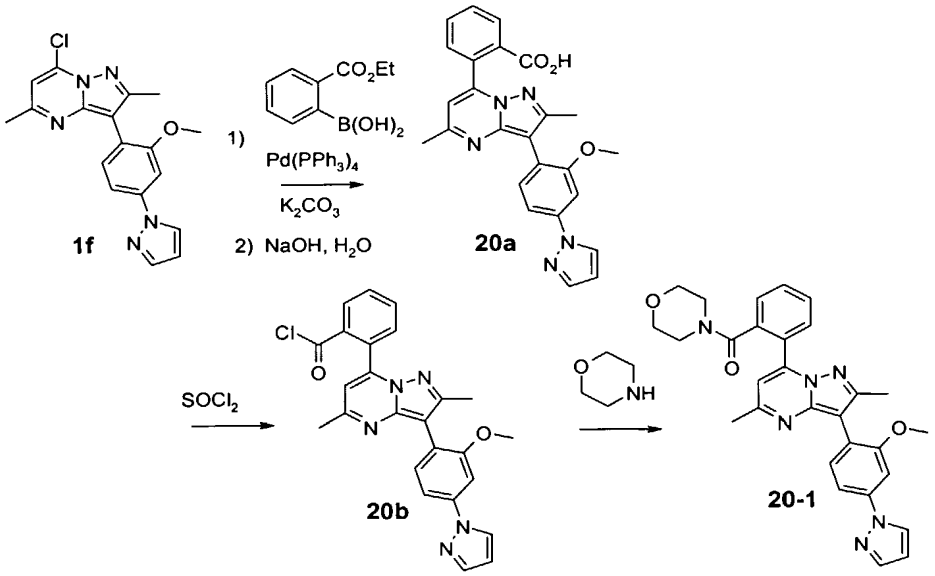



| Cmpd | $R_2$ | MW | MS | $t_R^*$ |
|---|---|---|---|---|
| **19-1** |  | 439.517 | 439 | 6.130 |

| Cmpd | $R_2$ | MW | MS | $t_R$* |
|---|---|---|---|---|
| 19-2 |  | 483.569 | 483 | 5.980 |
| 19-3 |  | 453.543 | 453 | 6.290 |

* All HPLC determinations employed Analytical Method 2.

## EXAMPLE 20




Step 20A:

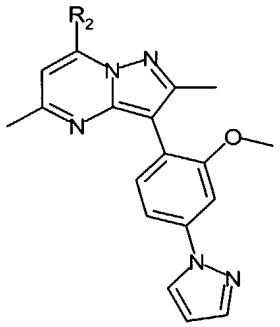
A mixture of Cmpd **1f** (710 mg, 2.0 mmol), (2-ethoxycarbonyl)phenylboronic acid (470 mg, 2.4 mmol), tetrakis (triphenylphosphine)palladium(0) (116 mg, 0.1 mmol), and potassium carbonate (550 mg, 4.0 mmol) was heated in 9:1 dioxane/water (10 mL) at 100 °C for 2.5 hr. Sodium hydroxide solution (3N, 10 mL) was added, and the mixture was stirred at 100 °C for an additional 30 min. The cooled mixture was concentrated, then water was added and the pH adjusted to 2 with hydrochloric acid. The mixture was extracted with chloroform, then the combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated to provide a crude solid, which was recrystallized from chloroform to provide Cmpd **20a** (420 mg, 48 % yield) as a yellow solid.

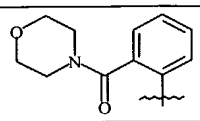
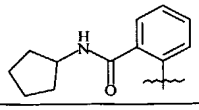
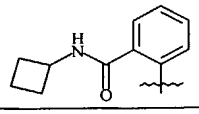
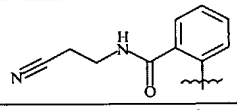
Step 20B:

Compound **20a** (420 mg, 0.96 mmol) was heated in 10 mL chloroform with thionyl chloride (1.0 mL, 14 mmol) at 70 °C for 2 hr. Volatiles were evaporated to provide Cmpd **20b** (450 mg) as a dark solid.

Step 20C:

A solution of **20b** (32 mg, 0.07 mmol) in chloroform (1 mL) was treated with morpholine (0.1 mL, 1 mmol) at RT. The mixture was allowed to sit at RT for 30 min, then the solvent was evaporated. The residue was taken up in methanol, filtered and purified directly by preparative HPLC/MS to provide **20-1** (13 mg, 30 %) as a TFA salt. Depending on the amine used, the compounds listed in the following table were synthesized and purified by preparative HPLC-MS:

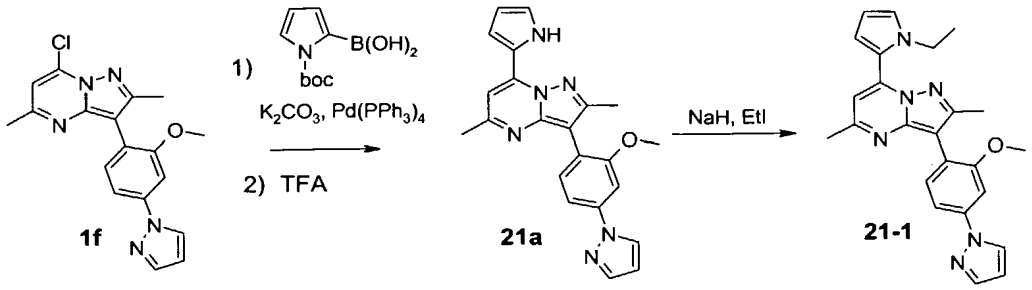


| Cmpd | $R_2$ | MW | MS | $t_R$* |
|---|---|---|---|---|
| **20-1** |  | 508.579 | 508 | 6.180 |
| **20-2** |  | 506.607 | 506 | 7.050 |
| **20-3** |  | 492.58 | 492 | 6.710 |
| **20-4** |  | 491.552 | 491 | 5.840 |

* All HPLC determinations employed Analytical Method 2.

## EXAMPLE 21

7-(1-ETHYL-1H-PYRROL-2-YL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE




Step 21A:

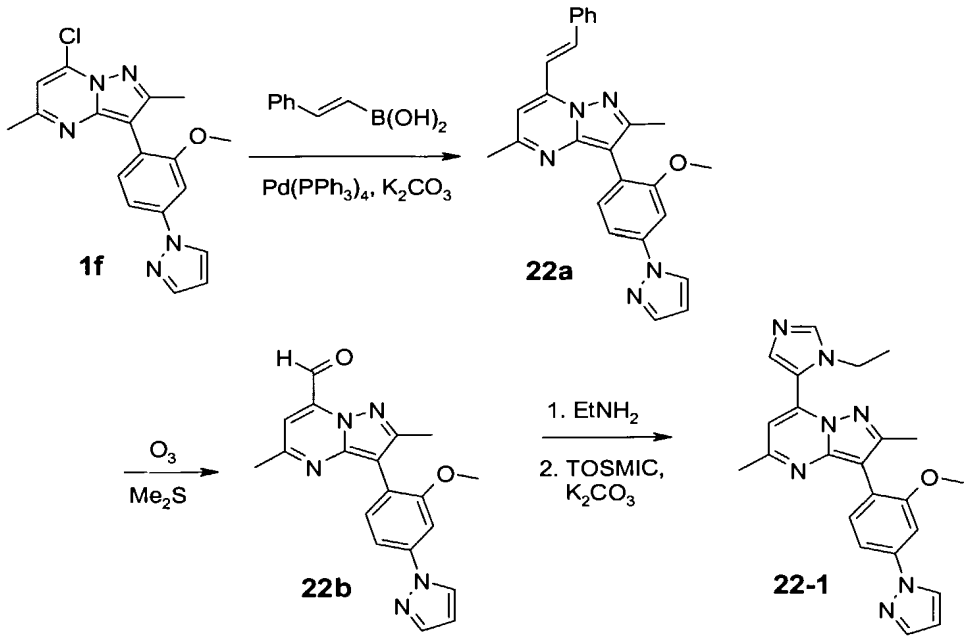
A mixture of Cmpd **1f** (210 mg, 0.6 mmol), N-Boc-pyrrole-2-boronic acid (158 mg, 0.75 mmol), tetrakis(triphenylphosphine)palladium(0) (40mg, 0.035 mmol), and potassium carbonate (166 mg, 1.2 mmol) was heated in 9:1 dioxane/water (5 mL) at 110 °C for 3 hr in a sealed tube. The cooled mixture was concentrated, then water was added and the mixture was extracted with chloroform. The combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated to provide a crude solid, which was stirred in 1:1 TFA/DCM (3 mL) for 16 hr. The mixture was diluted with ethyl acetate, then treated with aqueous ammonia. The organic layer was dried over sodium sulfate, filtered, and concentrated, then the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent to provide **21a** (110 mg, 48 % yield) as a yellow solid.

Step 21B:

To a solution of **21a** (110 mg, 0.28 mmol) in dry DMF (2 mL) was added sodium hydride (20 mg of a 60% dispersion in mineral oil, 0.5 mmol) at RT. The mixture was stirred for 5 min, then ethyl iodide (0.050 mL, 0.60 mmol) was added and the mixture was stirred at RT for 2 hr. Water and ethyl acetate were added, then the ethyl acetate layer was washed with water and brine, then dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluent to provide Cmpd **21-1** (84 mg, 73 % yield) as a yellow solid; MW: 412.50 LC/MS: 412 $[MH]^+$; $t_R$: 7.630, Anal. Meth. 2.

## EXAMPLE 22

7-(3-ETHYL-3H-IMIDAZOL-4-YL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE




Step 22A:

A mixture of Cmpd **1f** (1.50 g, 4.25 mmol), 2-phenylethenylboronic acid (692 mg, 4.68 mmol), potassium carbonate (1.17 g, 8.50 mmol), and tetrakis (triphenylphosphine)palladium(0) (250 mg, 0.22 mmol) in dioxane (9 mL) and water (1 mL) was heated at 105 °C for 16 hr. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated, and the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent to afford **22a** (1.60 g, 89 % yield) as a yellow solid.

Step 22B:

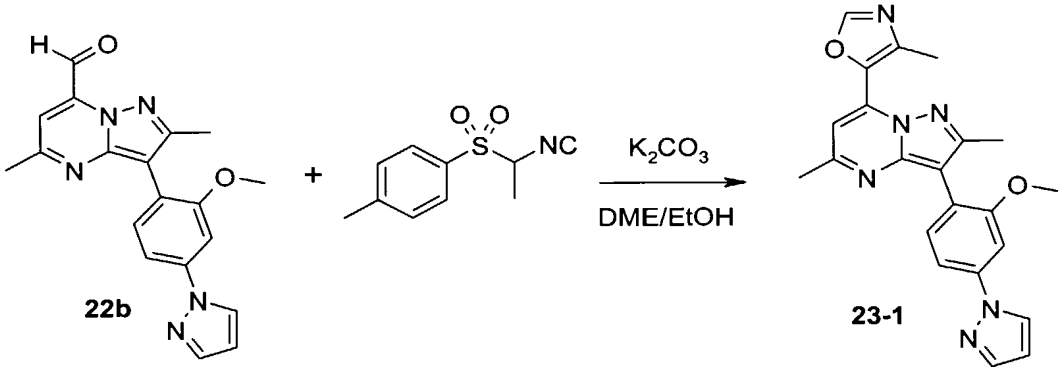
An ozone/oxygen mixture was bubbled through a solution of **22a** (1.60 g, 3.8 mmol) in dry 2:1 DCM/methanol (20 mL) at – 70 °C for 8 minutes. Dimethyl sulfide (1.5 mL) was added and the mixture was stirred and allowed to warm to RT over 16 hr. The solvent was evaporated and the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent, providing Cmpd **22b** (1.0 g, 76 % yield) as a yellow solid.

Step 22C:

A mixture of **22b** (35 mg, 0.10 mmol), ethylamine (1.0 mL of a 2.0M solution in THF, 2.0 mmol), and magnesium sulfate in 1,2-dichloroethane was stirred at RT for 15 hr. The mixture was filtered, then the filtrate was evaporated to dryness. The residue was taken up in 1:1 ethanol/DME (2 mL), then TOSMIC (38 mg, 0.19 mmol) and potassium carbonate (55 mg, 0.4 mmol) were added and the mixture was refluxed for 17 hr. Water was added and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluent, providing Cmpd **22-1** (5 mg) as an oil; MW: 413.48 LC/MS: 413 $[MH]^+$; $t_R$: 5.000, Anal. Meth. 2.

## EXAMPLE 23

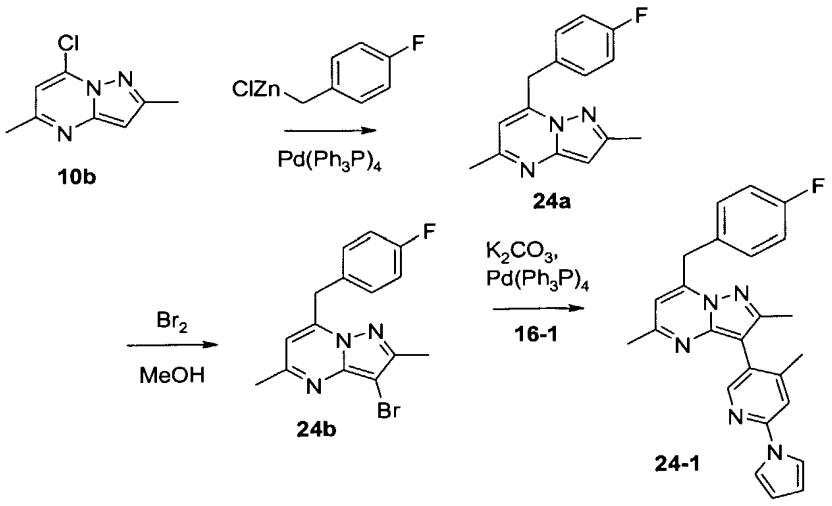
3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(4-METHYL-OXAZOL-5-YL)-PYRAZOLO[1,5-A]PYRIMIDINE




A mixture of **22b** (208 mg, 0.60 mmol), alpha-methyl-TOSMIC (251 mg, 1.2 mmol) and potassium carbonate (248 mg, 1.8 mmol) was heated in 5 mL 1:1 DME/ethanol at 80 °C for 14 hr. Water was added and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluent, providing **23-1** (60 mg, 23 %) as an oil; MW: 400.44 LC/MS: 400 $[MH]^+$; $t_R$: 5.250, Anal. Meth. 2.

## EXAMPLE 24

7-(4-FLUORO-BENZYL)-2,5-DIMETHYL-3-(4-METHYL-6-PYRROL-1-YL-PYRIDIN-3-YL)-PYRAZOLO[1,5-A]PYRIMIDINE




Step 24A:

To a solution of 4-fluorophenylzinc chloride (20 mL of a 0.5 M solution in THF, 10 mmol) were added Cmpd **10b** (1.0 g, 5.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.26 mmol). The reaction mixture was heated at 90 °C in a sealed tube for 3 hr. The cooled reaction mixture was treated with 4N hydrochloric acid (4 mL), then water was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with 30% ethyl acetate in hexanes to obtain **24a** (1.0 g, 71 % yield) as an off-white solid.

Step 24B:

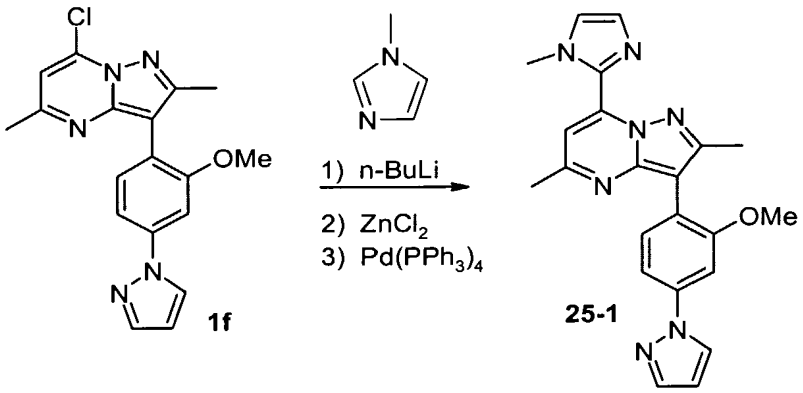
Compound **24a** (1.0 g, 3.9 mmol) was dissolved in 15 mL methanol. Bromine (0.62 g, 3.9 mmol) was added dropwise to the solution, resulting in formation of a white precipitate. The solid was collected on a fritted glass filter and rinsing with methanol. This compound was further purified by silica gel column chromatography, eluting with 4:1 hexanes/ethyl acetate to provide first a dibromination product (110 mg, 7 % yield), followed by **24b** (1.0 g, 77 % yield) as a white solid.

Step 24C:

A mixture of Cmpd **24b** (800 mg, 2.4 mmol), Cmpd **16-1** (500 mg, 2.5 mmol), tetrakis(triphenylphosphine)palladium(0) (280 mg, 0.24 mmol), and potassium carbonate (600 mg, 4.3 mmol) was heated in 9:1 dioxane/water (3.5 mL) at 95 °C for 3 hr in a sealed tube. Aqueous sodium bicarbonate solution (5 mL) was added to the cooled mixture, which was then extracted twice with DCM. The combined DCM extracts were dried over sodium sulfate, filtered, and concentrated to provide a crude oil, which was partially purified by prep HPLC/MS. The partially purified product was then chromatographed on silica gel using 4:1 hexanes/ethyl acetate as eluent, providing Cmpd **24-1** (3 mg) as a yellow solid; MW: 411.48 LC/MS: 412 $[MH]^+$; $t_R$: 9.160, Anal. Meth. 2.

## EXAMPLE 25

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(1-METHYL-1H-IMIDAZOL-2-YL)-PYRAZOLO[1,5-A]PYRIMIDINE



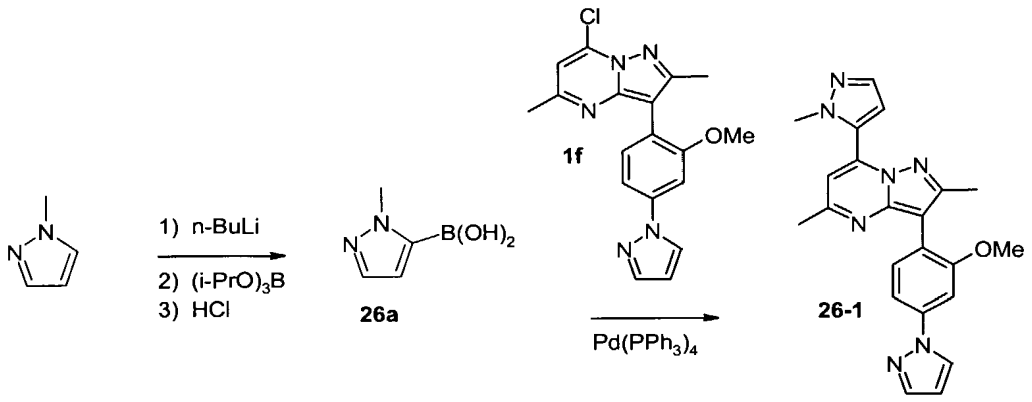

Step 25A:

To a solution of 1-methylimidazole (246 mg, 3.0 mmol) in dry THF (3 mL) cooled to –70 °C was added n-BuLi (2.5 M solution in hexane, 1.7 mL, 4.2 mmol) dropwise. The reaction mix was stirred at – 70 °C for 10 min, then $ZnCl_2$ (0.5 M solution in THF, 20 mL, 10 mmol) was added over 5 min. The mixture was stirred at -70 °C for 1 hr, then was warmed to 0 °C. Cmpd **1f** (106 mg, 0.30 mmol) and tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol) were added. The mixture was then heated to reflux for 3 hr. The cooled reaction mixture was quenched with water, the THF was evaporated and the resulting aqueous mixture was extracted with

ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and the residue was chromatographed on silica gel using ethyl acetate as eluant to give **25-1** (15 mg) as a yellow solid; HPLC retention time 4.13 min (method 2); MW 399.5; observed MS 399.

## EXAMPLE 26

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(2-METHYL-2H-PYRAZOL-3-YL)-PYRAZOLO[1,5-A]PYRIMIDINE




Step 26A:

To a solution of 1-methylpyrazole (820 mg, 10 mmol) in dry THF (20 mL) cooled to – 70 °C was added n-BuLi (1.6 M solution in hexane, 6.3 mL, 10 mmol) dropwise. The reaction mix was stirred at –70 °C for 5 min, then triisopropyl borate (2.5 mL, 11 mmol) was added over 5 min. The mixture was allowed to warm to RT over 1 hr, then 6N hydrochloric acid (5 ml) was added. The mixture was stirred for 30 min, then was evaporated to dryness to provide crude **26a** as a solid, which was used without further purification.

Step 26B:

Cmpd **1f** (530 mg, 1.5 mmol) and crude **26a** (entire amount, approximately 10 mmol) were subjected to Suzuki reaction according to the procedure of Example 1. The reaction mixture was concentrated, then water was added and the mixture was extracted with chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated, then the residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluant. The product was further

purified by crystallization from acetonitrile, providing Cmpd **26-1** (280 mg) as a yellow solid; HPLC retention time 6.42 min (method 2); MW 399.5; observed MS 399)

## EXAMPLE 27

### CRF RECEPTOR BINDING ACTIVITY

The compounds of this invention may be evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by Grigoriadis et al. (*Mol. Pharmacol* vol50, pp679-686, 1996) and Hoare et al. (*Mol. Pharmacol* vol63 pp751-765, 2003.) By utilizing radiolabeled CRF ligands, the assay may be used to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype.

Briefly, the binding assay involves the displacement of a radiolabeled CRF ligand from the CRF receptor. More specifically, the binding assay is performed in 96-well assay plates using 1-10μg cell membranes from cells stably transfected with human CRF receptors. Each well receives about 0.05 mL assay buffer (*e.g.*, Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 2mM EGTA) containing compound of interest or a reference ligand (for example, sauvagine, urocortin I or CRF), 0.05 mL of [$^{125}$I] tyrosine - sauvagine (final concentration ~150 pM or approximately the $K_D$ as determined by Scatchard analysis) and 0.1 mL of a cell membrane suspension containing the CRF receptor. The mixture is incubated for 2 hr at 22 °C followed by separation of the bound and free radioligand by rapid filtration over glass fiber filters. Following three washes, the filters are dried and radioactivity (Auger electrons from $^{125}$I) is counted using a scintillation counter. All radioligand binding data may be analyzed using the non-linear least-squares curve-fitting programs Prism (GraphPad Software Inc) or XL*fit* (ID Business Solutions Ltd).

## EXAMPLE 28

### CRF-STIMULATED ADENYLATE CYCLASE ACTIVITY

The compounds of the present invention may also be evaluated by various functional testing. For example, the compounds of the present invention may be screened for CRF-stimulated adenylate cyclase activity. An assay for the determination of CRF-stimulated adenylate cyclase activity may be performed as

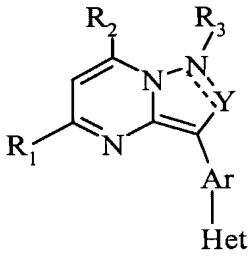
generally described by Battaglia et al. (*Synapse 1*:572, 1987) with modifications to adapt the assay to whole cell preparations.

More specifically, the standard assay mixture may contain the following in a final volume of 0.1 mL: 2 mM L-glutamine, 20 mM HEPES, and 1 mM IMBX in DMEM buffer. In stimulation studies, whole cells with the transfected CRF receptors are plated in 96-well plates and incubated for 30 min at 37 °C with various concentrations of CRF-related and unrelated peptides in order to establish the pharmacological rank-order profile of the particular receptor subtype. Following the incubation, cAMP in the samples is measured using standard commercially available kits, such as cAMP-Screen™ from Applied Biosystems. For the functional assessment of the compounds, cells and a single concentration of CRF or related peptides causing 50% stimulation of cAMP production are incubated along with various concentrations of competing compounds for 30 min at 37°C, and cAMP determined as described above.

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

WHAT IS CLAIMED IS:

1. A compound having the following structure:



or a pharmaceutically acceptable salt, ester, solvate, stereoisomer or prodrug thereof,

wherein:

"---" represents the second bond of an optional double bond;

$R_1$ is hydrogen, alkyl, substituted alkyl, heteroaryl, substituted heteroaryl, $-NH_2$, or halogen;

$R_2$ is alkyl, substituted alkyl, $-C(O)NR_7R_8$, aryl, substituted aryl, aryloxyalkyl, substituted aryloxyalkyl, heteroarylalkoxyalkyl, substituted heteroarylalkoxyalkyl, heterocyclealkyl, substituted heterocyclealkyl, arylalkyl, substituted arylalkyl, heteroaryl, or substituted heteroaryl, wherein said heteroaryl or substituted heteroaryl is connected to the pyrimidine ring via a carbon-carbon bond;

$R_3$ is null, hydrogen, or alkyl;

Y is $=(CR_4)-$ or $-(C=O)-$;

$R_4$ is hydrogen, alkyl, substituted alkyl, thioalkyl, alkylsulfinyl, or alkylsulfonyl;

Ar is phenyl, phenyl substituted with 1 or 2 $R_5$, pyridyl or pyridyl substituted with 1 or 2 $R_5$;

$R_5$ at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, alkylsulfonyl, or alkylsulfinyl;

Het is heteroaryl optionally substituted with 1 or 2 $R_6$;

$R_6$ at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen; and

$R_7$ and $R_8$ are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, arylalkyl, substituted arylalkyl, heterocyclealkyl or substituted heterocyclealkyl; or

$R_7$ and $R_8$ taken together with the nitrogen to which they are attached form a heterocyclic ring or a substituted heterocyclic ring.

2. A compound according to claim 1 wherein $R_1$ is hydrogen, alkyl, substituted alkyl, $-NH_2$, or halogen.

3. A compound according to claim 1 wherein $R_2$ is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, wherein said heteroaryl or substituted heteroaryl is connected to the pyrimidine ring via a carbon-carbon bond.

4. A compound according to claim 1 wherein $R_3$ is null.

5. A compound according to claim 4 wherein Y is $=(CR_4)-$.

6. A compound according to claim 5 wherein $R_4$ is hydrogen, alkyl, or substituted alkyl.

7. A compound according to claim 1 wherein $R_3$ is hydrogen or alkyl.

8 A compound according to claim 7 wherein Y is $-(C=O)-$.

9. A compound according to claim 1 wherein Ar is phenyl substituted with 1 $R_5$.

10. A compound according to claim 9 wherein $R_5$ is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, alkylsulfonyl, or alkylsulfinyl.

11. A compound according to claim 1 wherein Het is substituted with 1 $R_6$.

12. A compound according to claim 11 wherein $R_6$ is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen.

13. A compound according to claim 1,

wherein:

$R_1$ is hydrogen, alkyl or substituted alkyl;

$R_3$ is null;

Y is $=(CR_4)-$;

$R_4$ is hydrogen, alkyl or substituted alkyl;

Ar is phenyl substituted with one $R_5$;

$R_5$ is alkyl, aubstituted alkyl, alkoxy or substituted alkoxy; and

Het is heteroaryl.

14. A compound according to claim 13,

wherein:

$R_1$ is lower alkyl;

$R_4$ is lower alkyl;

$R_5$ is alkoxy; and

Het is pyrazolyl.

15. A compound according to claim 14,

wherein:

$R_1$ is methyl;

$R_4$ is methyl; and

$R_5$ is methoxy.

16. A compound according to claim15,

wherein:

$R_2$ is alkyl, substituted arylalkyl, substituted aryl, heteroaryl, substituted heteroaryl, substituted heteroaryloxyalkyl, heteroarylalkyl or substituted heteroarylalkyl.

17. A compound according to claim 16,

wherein:

$R_2$ is substituted arylalkyl, substituted aryl, heteroaryl or substituted heteroaryl.

18. A compound according to claim 17,

wherein:

$R_2$ is substituted benzyl, substituted phenyl, substituted pyrazolyl, pyridinyl or substituted pyridinyl.

19. A compound according to claim 18,

wherein:

$R_2$ is substituted pyrazolyl, pyridinyl or substituted pyridinyl.

20. A compound according to claim 19,

wherein:

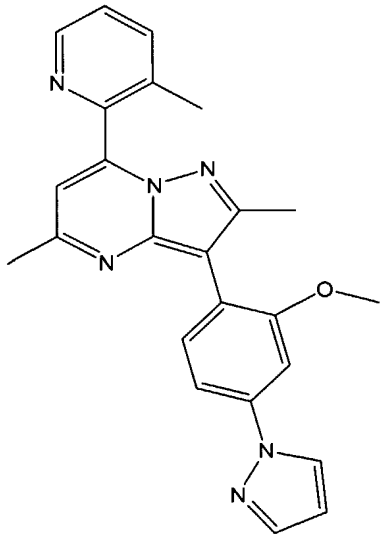
$R_2$ is substituted pyridinyl.

21. A compound according to claim 20,

wherein:

$R_2$ is methyl substituted pyridinyl or methoxy substituted pyridinyl.

22. A compound according to claim 21, wherein said compound is represented by the formula:



23. A pharmaceutical composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent.

24. A method for treating a disorder manifesting hypersecretion of CRF in a mammal comprising administering to the animal an effective amount of a pharmaceutical composition according to claim 23.

25. A method according to claim 24, wherein the disorder is stroke.

26. A method according to claim 24, wherein the disorder is depression.

27. A method according to claim 24, wherein the disorder is an anxiety-related disorder.

28. A method according to claim 24, wherein the disorder is obsessive-compulsive disorder.

29. A method according to claim 24, wherein the disorder is irritable bowel syndrome.

30. A method according to claim 24, wherein the disorder is anorexia nervosa.

# INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/IB2004/004234

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No |
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☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex.

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 June 2005 | 27/06/2005 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx 31 651 epo nl,<br>Fax (+31–70) 340–3016 | Wolf, C |

Form PCT/ISA/210 (second sheet) (January 2004)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/004234

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: claims 24-30 in respect of industrial applicability
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 24-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/IB2004/004234

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Information on patent family members

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PCT/IB2004/004234

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International Bureau

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(10) International Publication Number
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(71) Applicant: **BRISTOL-MYERS SQUIBB PHARMA COMPANY** [US/US]; Patent Department, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(72) Inventor: **GILLIGAN, Paul, J.**; 2629 Pennington Drive, Wilmington, DE 19810 (US).

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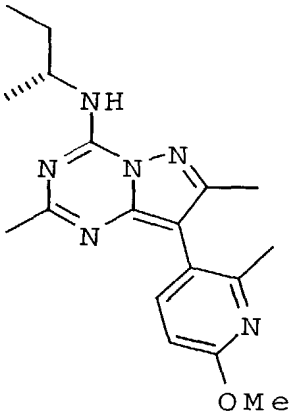
(54) Title: 4-(2-BUTYLAMINO)-2,7-DIMETHYL-8-(2-METHYL-6-METHOXYPYRID-3-YL) PYRAZOLO-[1,5-A]-1,3,5-TRIAZINE, ITS ENANTIOMERS AND PHARMACEUTICALLY ACCEPTABLE SALTS AS CORTICOTROPIN RELEASING FACTOR RECEPTOR LIGANDS




(I)

(57) Abstract: Corticotropin releasing factor (CRF) antagonists of Formula (I), and its use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

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# 4-(2-BUTYLAMINO)-2,7-DIMETHYL-8-(2-METHYL-6-METHOXYPYRID-3-YL)PYRAZOLO-[1,5-A]-1,3,5-TRIAZINE, ITS ENANTIOMERS AND PHARMACEUTICALLY ACCEPTABLE SALTS AS CORTICOTROPIN RELEASING FACTOR RECEPTOR LIGANDS

## Field of the Invention

This invention relates to a treatment of psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psycho-pathological disturbances and stress, by administration of 4-(2-Butylamino)-2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)pyrazolo-[1,5-a]-1,3,5-triazine, its enantiomer and pharmaceutically acceptable salts as a corticotropin releasing factor receptor ligand.

## Background of the Invention

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin (POMC) - derived peptide secretion from the anterior pituitary gland [J. Rivier et al., Proc. Nat. Acad. Sci. (USA) 80:4851 (1983); W. Vale et al., Science 213:1394

(1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., Rec. Prog. Horm. Res. 39:245 (1983); G.F. Koob, Persp. Behav. Med. 2:39 (1985); E.B. De Souza et al., J. Neurosci. 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, Physiological Reviews 69:1 (1989); J.E. Morley, Life Sci. 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, Hosp. Practice 23:59 (1988)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebrospinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., Science 226:1342 (1984); C.M. Banki et al., Am. J. Psychiatry 144:873 (1987); R.D. France et al., Biol. Psychiatry 28:86 (1988); M. Arato et al., Biol Psychiatry 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., Arch. Gen. Psychiatry 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., Am J. Psychiatry 141:619 (1984); F. Holsboer et al., Psychoneuroendocrinology 9:147 (1984); P.W. Gold et al., New Eng. J. Med. 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, Arch. Gen. Psychiatry 46:1047 (1989)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in

brain [Grigoriadis et al., Neuropsychopharmacology 2:53 (1989)].

It has also been postulated that CRF has a role in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., Life Sci. 31:363 (1982); C.W. Berridge and A.J. Dunn Regul. Peptides 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist a-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn Horm. Behav. 21:393 (1987), Brain Research Reviews 15:71 (1990)].

Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., Psychopharmacology 86:170 (1985); K.T. Britton et al., Psychopharmacology 94:306 (1988)] and in the acoustic

startle test [N.R. Swerdlow et al., Psychopharmacology 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., Psychopharmacology 94:306 (1988)].

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (a-helical CRF9-41) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

It has been further postulated that CRF has a role in cardiovascular or heart-related diseases as well as

gastrointestinal disorders arising from stress such as hypertension, tachycardia and congestive heart failure, stroke, irritable bowel syndrome post-operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress [for reviews see E.D. DeSouza, C.B. Nemeroff, Editors; Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990) and C. Maillot, M. Million, J.Y. Wei, A. Gauthier, Y. Tache, Gastroenterology, 119, 1569-1579 (2000)].

Over-expression or under -expression of CRF has been proposed as an underlying cause for several medical disorders. Such treatable disorders include, for example and without limitation: affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers,

amyotrophic lateral sclerosis, hypoglycemia, hypertension, tachycardia and congestive heart failure, stroke, osteoporosis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress [for reviews see J.R. McCarthy, S.C. Heinrichs and D.E. Grigoriadis, Cuur. Pharm. Res., 5, 289-315 (1999); P.J. Gilligan, D.W. Robertson and R. Zaczek, J. Medicinal Chem., 43, 1641-1660 (2000), G. P. Chrousos, Int. J. Obesity, 24, Suppl. 2, S50-S55 (2000); E. Webster, D.J. Torpy, I.J. Elenkov, G.P. Chrousos, Ann. N.Y. Acad. Sci., 840, 21-32 (1998); D.J. Newport and C.B. Nemeroff, Curr. Opin. Neurobiology, 10, 211-218 (2000); G. Mastorakos and I. Ilias, Ann. N.Y. Acad. Sci., 900, 95-106 (2000); M.J. Owens and C.B. Nemeroff, Expert Opin. Invest. Drugs, 8, 1849-1858 (1999); G. F. Koob, Ann. N.Y. Acad. Sci., 909, 170-185 (2000)].

The following publications each describe CRF antagonist compounds; however, none disclose the compounds provided herein: WO95/10506; WO99/51608; WO97/35539; WO99/01439; WO97/44308; WO97/35846; WO98/03510; WO99/11643; PCT/US99/18707; WO99/01454; and, WO00/01675.

Summary of the Invention

In accordance with one aspect, the present invention provides a novel compound, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections;

neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and

addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism; and hypoglycemia in a mammal.

The present invention provides a novel compound that binds to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compound of the present invention is useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a mammal.

According to another aspect, the present invention provides a novel compound of Formula (I) (described below) which is useful as an antagonist of the corticotropin releasing factor. The compound of the present invention exhibits activity as a corticotropin releasing factor antagonist and appears to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such a compound of Formula (I), and methods of using such a compound for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

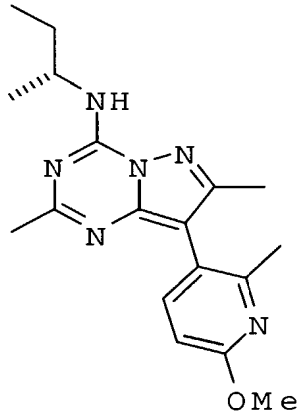
The use of competitive binding assays is considered particularly valuable for screening candidates for new drugs, e.g. to identify new CRF ligands or other compounds having even greater or more selective binding affinity for CRF receptors, which candidates would therefore be potentially useful as drugs. In the assay, one determines the ability of the candidate ligand to displace the labelled compound.

Therefore, another embodiment of the invention includes the use of a compound of the invention is a binding assay, wherein one or more of the compounds may be joined to a label, where the label can directly or indirectly provide a detectable signal. Various labels include radioisotopes, fluorescers, chemiluminescers, specific binding molecules, particles, e.g. magnetic particles, and the like.

Another embodiment of the invention is directed to the use of the compounds of the invention (particularly labeled compounds of this invention) as probes for the localization of receptors in cells and tissues and as standards and reagents for use in determining the receptor-binding characteristics of test compounds. Labeled compounds of the invention may be used for in vitro studies such as autoradiography of tissue sections or for in vivo methods, e.g. PET or SPECT scanning. Particularly, preferred compounds of the invention are useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF1 receptor.

Detailed Description of the Invention

[1] In a first embodiment, the present invention provides a compound of Formula (I):




(I)

and stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[2] In another embodiment, the present invention provides a compound of embodiment [1], isomers thereof, stereoisomeric forms thereof, mixtures of stereoisomeric forms thereof, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms thereof, wherein said compound is 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine or 4-((S)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

[3] In another embodiment, the present invention provides a compound of any one of embodiments [1] to [2], pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms thereof, wherein

said compound is substantially free of its (S) stereoisomer

[4] In another embodiment, the present invention provides a compound of embodiment [1], wherein said compound is 4-(2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

[5] In another embodiment, the present invention provides a compound of embodiment [1], wherein said compound is 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

[6] A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

[7] In another embodiment, the present invention provides a method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

[8] In another embodiment, the present invention provides a method of treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal, comprising administering to the animal a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

[9] In another embodiment, the present invention provides a method for the treatment of a disorder, the treatment of which can be effected or facilitated by antagonizing CRF, comprising administering to the mammal

a therapeutically effective of a compound of any one of embodiments [1] to [5].

[10] In another embodiment, the present invention provides a method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

[11] In another embodiment, the present invention provides a method of treating anxiety or depression in mammals, comprising administering to the mammal a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

[12] In another embodiment, the present invention provides a method for screening for ligands for CRF receptors, which method comprises:

a) carrying out a competitive binding assay with a CRF receptor, a compound of any one of embodiments [1] to [5] which is labelled with a detectable label, and a candidate ligand; and

b) determining the ability of said candidate ligand to displace said labelled compound.

[13] In another embodiment, the present invention provides a method for detecting CRF receptors in tissue comprising:

a) contacting a compound of any one of embodiments [1] to [5], which is labelled with a detectable label, with a tissue, under conditions that permit binding of the compound to the tissue; and

b) detecting the labelled compound bound to the tissue.

[14] In another embodiment, the present invention provides a method of inhibiting the binding of CRF to a CRF-1 receptor, comprising contacting a compound of any one of embodiments [1] to [5] with a solution comprising cells expressing the CRF1 receptor, wherein the compound is present in the solution at a concentration sufficient to inhibit the binding of CRF to the CRF-1 receptor.

[15] In another embodiment, the present invention provides a article of manufacture comprising:

a) a packaging material;

b) a compound of any one of embodiments [1] to [5]; and

c) a label or package insert contained within said packaging material idicating that said compound is effective for treating anxiety or depression.

[16] The present invention also comprises a method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers,

amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of any one of embodiments [1] to [5].

Definitions

As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Suitable non-toxic acids include inorganic and organic acids of basic residues such as amines, for example, acetic, benzenesulfonic, benzoic, amphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like; and alkali or organic salts of acidic residues such as carboxylic acids, for example, alkali and alkaline earth metal salts derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, trimethylammonia, triethylammonia, ethylenediamine, n-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine,chloroprocaine, diethanolamine, procaine, n-benzylphenethylamine,

diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide,and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Pharmaceutically acceptable prodrugs" as used herein means any covalently bonded carriers which release the active parent drug of Formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of Formula (I) are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" means compounds that are rapidly transformed *in vivo* to

yield the parent compound of formula (I), for example by hydrolysis in blood. Functional groups which may be rapidly transformed, by metabolic cleavage, in vivo form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as alkanoyl (such as acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethysilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds useful according to this invention are cleaved in vivo, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion of prodrugs is provided in the following: Design of Prodrugs, H. Bundgaard, ed., Elsevier, 1985; Methods in Enzymology, K. Widder et al, Ed., Academic Press, 42, p.309-396, 1985; A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard, ed., Chapter 5; "Design and Applications of Prodrugs" p.113-191, 1991; Advanced Drug Delivery Reviews, H. Bundgard, 8, p.1-38, 1992; Journal of Pharmaceutical Sciences, 77, p. 285, 1988; Chem. Pharm. Bull., N. Nakeya et al, 32, p. 692,

1984; Pro-drugs as Novel Delivery Systems, T. Higuchi and V. Stella, Vol. 14 of the A.C.S. Symposium Series, and Bioreversible Carriers in Drug Design, Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, 1987, which are incorporated herein by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of Formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of Formula (I) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula (I), and the like.

As used herein to describe a compound, the term "substantially free of its (S) stereoisomer" means that the compound is made up of a significantly greater proportion of its (R) stereoisomer than of its optical antipode (i.e., its (S) stereoisomer). In a preferred embodiment of the invention, the term "substantially free of its (S) stereoisomer" means that the compound is made up of at least about 90% by weight of its (R)

stereoisomer and about 10% by weight or less of its (S) stereoisomer.

In a more preferred embodiment of the invention, the term "substantially free of its (S) stereoisomer" means that the compound is made up of at least about 95% by weight of its (R) stereoisomer and about 5% by weight or less of its (S) stereoisomer. In an even more preferred embodiment, the term "substantially free of its (S) stereoisomer" means that the compound is made up of at least about 99% by weight of its (R) stereoisomer and about 1% or less of its (S) stereoisomer. In another preferred embodiment, the term "substantially free of its (S) stereoisomer" means that the compound is made up of nearly 100% by weight of its (R) stereoisomer. The above percentages are based on the total amount of the combined stereoisomers of the compound.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

As used herein, the term "labeled" is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, e.g. radioisotope, fluorescers, enzyme, antibodies, particles such as magnetic particles, chemiluminescer, $P^{32}$, $I^{131}$, and $At^{211}$, etc.

Syntheses

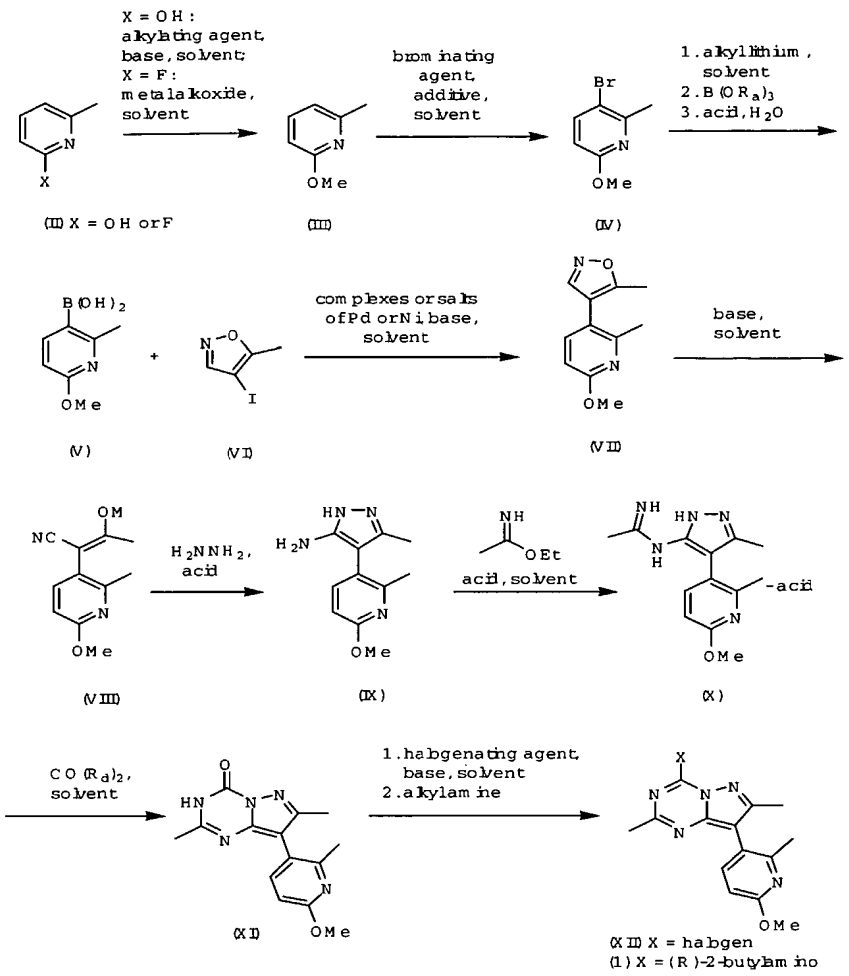
Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and 1 or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture.

The present invention includes all stereoisomeric forms of the compounds of the formula I. Centers of asymmetry that are present in the compounds of formula I can all independently of one another have S configuration or R configuration. The prefixes d and 1 or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or

diastereomers, in all ratios. Thus, enantiomers are a subject of the invention in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both the cis form and the trans form as well as mixtures of these forms in all ratios. The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials for the synthesis or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compounds of the formula I or at the stage of an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of formula (I).

The compound of Formula (I) may be prepared from using the procedures outlined in Scheme 1.

Scheme 1




A compound of Formula (II), where X = F, may be treated with a metal alkoxide (e.g. sodium methoxide, potassium methoxide; pre-formed or generated in situ) in an inert solvent to generate an intermediate of Formula (III). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably

tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Alternatively, a compound of Formula (II), where X = OH, may be treated with an alkylating agent in the presence of a base in an inert solvent to generate an intermediate of Formula (III). Alkylating agents include, but are not limited to, haloalkanes (e.g. $CH_3I$), dialkyl sulfates (e.g. $Me_2SO_4$) or alkyl trifluoro-sulfonates (e.g. $CH_3O_3SCF_3$).

Bases may include, but are not limited to, alkali metals, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal carbonates, alkaline metal carbonates, transition metal carbonates (e.g. silver carbonate), alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bicarbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine).

Inert solvents may include, but are not limited to, halocarbons (1 to 8 carbons, 1 to 8 halogens), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 50°C to 150°C.

A compound of Formula (III) may be transformed to a compound of Formula (IV) by reaction with a brominating agent in the presence or absence of an additive in an inert solvent. Brominating agents include, but are not limited to, N-bromosuccinimide - 2,2'-azobisisobutyronitrile (AIBN), N-bromophthalimide - 2,2'-azobisisobutyronitrile (AIBN)), bromine. Additives include, but are not limited to, alkali metal phosphates (e.g. $K_3PO_4$, $Na_3PO_4$), alkali metal hydrogen phosphates (e.g. $Na_2HPO_4$, $K_2HPO_4$), alkali metal dihydrogen phosphates (e.g. $NaH_2PO_4$, $KH_2PO_4$). Inert solvents include, but are not

limited to, halocarbons (1 to 6 carbons, 1 to 6 halogens (preferably chlorine), water, N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one). Reaction temperatures range from 0°C to 200°C (preferably 20°C to 120°C).

A compound of Formula (IV) may be converted to a compound of Formula (V) by sequential reactions with (1) an alkyl lithium in an inert solvent at temperatures ranging from -100°C to 50°C; (2) a compound of the Formula $B(OR^a)_3$ ( where $R^a$ is branched or straight chain alkyl of 1 to 20 carbons) at temperatures ranging from -100°C to 50°C and (3) an acid in the presence or absence of water at temperatures ranging from -100°C to 100°C. Alkyl lithiums may be branched or straight chain compounds containing 1 to 20 carbons. Inert solvents include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or aromatic hydrocarbons (preferably benzene or toluene).

Acids may include, but are not limited to, alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably

p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid.

A compound of Formula (VII) may be produced by reaction of a compound of Formula (V) with a compound of Formula (VI) in the presence of a complex or salt of palladium or nickel, a base and an inert solvent. Complexes of palladium or nickel include, but are not limited to, phosphine complexes such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $NiCl_2(PPh_3)_2$, or [1,1-bis(diphenylphosphino)ferrocene]-dichloropalladium. Bases may include, but are not limited to, alkali metals, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkali metal carbonates, alkaline metal carbonates (e.g. barium carbonate), transition metal carbonates (e.g. silver carbonate) or trialkyl amines (e.g. triethyl amine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -100°C to 100°C.

An intermediate of Formula (VII) may be reacted with a base in the presence of an inert solvent to afford a compound of Formula (VIII), where M is an alkali metal cation (e.g. sodium or potassium). Bases may include, but are not limited to, alkali metal hydroxides (e.g. NaOH or KOH), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide) or alkaline earth metal hydroxides. Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide). Preferred reaction temperatures range from 0°C to 150°C.

Compounds of Formula (VIII) may be treated with hydrazine-hydrate in the presence of an acid and an inert solvent at temperatures ranging from 0°C to 200°C, preferably 70°C to 150°C, to produce compounds of Formula (IX). Acids may include, but are not limited to, alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic

acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid.

Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene).

A compound of Formula (IX) may be reacted with compounds of Formula $H_3C(C=NH)OR^c$ (where $R^c$ is alkyl (1-6 carbons)) in the presence or absence of an acid in the presence of an inert solvent at temperatures ranging from $0^oC$ to $200^oC$ to produce a compound of Formula (X). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably

methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used.

Inert solvents may include, but are not limited to, water, alkanenitriles (1 to 6 carbons, preferably acetonitrile), halocarbons of 1 to 6 carbons and 1 to 6 halogens (preferably dichloroethane or chloroform), alkyl alcohols of 1 to 10 carbons (preferably ethanol), dialkyl ethers (4 to 12 carbons, preferably diethyl ether or di-isopropylether) or cyclic ethers such as dioxan or tetrahydrofuran. Preferred temperatures range from 0°C to 100°C.

A compound of Formula (X) may be converted to an intermediate compound of Formula (XI) by treatment with compounds $C{=}O(R^d)_2$ (where $R^d$ is halogen (preferably chlorine), alkoxy (1 to 4 carbons) or alkylthio (1 to 4 carbons)) in the presence or absence of a base in an inert solvent at reaction temperatures from -50°C to 200°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkali metal carbonates, alkali metal hydroxides, trialkyl amines (preferably N,N-di-

isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine).

Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene).

A compound of Formula (XI) may be treated with a halogenating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give a halogenated intermediate (XII) (where X is halogen). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, $PCl_3$, $PCl_5$, $POBr_3$, $PBr_3$ or $PBr_5$. Bases may include, but are not limited to, trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably N,N-diethylaniline).

Inert solvents may include, but are not limited to, N,N-dialkylformamides (preferably dimethylformamide),

N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 20°C to 200°C.

A compound of Formula (XII) may be reacted with an alkyl amine in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80 to 250°C to generate compounds of Formula (I). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine).

Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably

tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloroethane). Preferred reaction temperatures range from 0°C to 140°C.

The compounds of the invention may be prepared as radiolabeled compounds by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably $^{14}C$), hydrogen (preferably $^{3}H$), sulfur (preferably $^{35}S$), or iodine (preferably $^{125}I$). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, Ill.; Cambridge Isotope Laboratories, Inc. Andover, Mass.; SRI International, Menlo Park, Calif.; Wizard Laboratories, West Sacramento, Calif.; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St.Louis, Mo.; and Moravek Biochemicals Inc., Brea, Calif.

Tritium labeled probe compounds may also conveniently be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-

catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate.

Receptor autoradiography (receptor mapping) may be carried out in vitro as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention.

## EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on a Varian VXR or Unity 300 FT-NMR instruments(300 MHz); chemical shifts were recorded in ppm ($\delta$) from an internal tetramethysilane standard in deuterochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer or a Hewlett Packard 5988A model spectrometer (using chemi-ionization (CI) with $NH_3$ as the carrier gas,

electrospray (ESI), atmospheric pressure chemi-ionization (APCI) or gas chromatography (GC)). Melting points were recorded on a MelTemp 3.0 heating block apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper.

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to the general procedures outlined by D. Perrin and W.L.F. Armarego, Purification of Laboratory Chemicals, 3rd ed., (New York: Pergamon Press, 1988). Chromatography was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight. Commonly used abbreviations are: DMF (N,N-dimethylformamide), EtOH (ethanol), MeOH (methanol), EtOAc (ethyl acetate), HOAc (acetic acid), DME (1,2-diethoxyethane) and THF (tetrahydrofuran).

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

EXAMPLE 1

Preparation of 2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-[1,3,5]-triazin-4(3H)-one

A. 2-Methoxy-6-methylpyridine.

Sodium (31.0 g, 1.35 mol) was added portionwise to methanol (500 mL) over 30 min with stirring in a flask equipped with a reflux cindenser. After the addition was complete, the reaction mixture was allowed to cool to ambient temperature. 2-Fluoro-6-methylpyridine (50 g, 450 mmol) was added portionwise with stirring. The reaction mixture was then heated to reflux temperature and stirred for 48 h. The mix was then cooled to ambient temperature and solvent was removed in vacuo to provide a yellow oil. The residue was taken up in water (500 mL) and three extractions with ether (200 mL) were performed. The combined organic layers were dried over $MgSO_4$, filtered and solvent was removed in vacuo from the filtrate to give a yellow liquid: $^1$H-NMR($CDCl_3$, 300 MHz): $\delta$ 7.44 (dd, 1H, J = 8, 7), 6.71 (d, 1H, J = 7), 6.53 (d, 1H, J = 8), 3.91 (s, 3H), 2.45 (s, 3H).

B. 2-Methoxy-6-methylpyridine.

A mixture of 2-hydroxy-6-methylpyridine (6.85 g, 62.8 mmol), silver carbonate (22.5 g, 81.6 mmol), iodomethane (39.1 mL, 628 mmol) and chloroform (200 mL) was stirred at ambient temperature for 40 h in the dark. The reaction mixture was filtered through celite. The

collected solid was washed with ether. The combined filtrates were concentrated in vacuo to give a liquid (6.25 g), which was identical to the product from Part A.

C. 6-Methoxy-3-bromo-2-methylpyridine.

A mixture of 2-methoxy-6-methylpyridine (17.0 g, 138 mmol) and a solution of disodium hydrogen phosphate (0.15M in water, 250 mL) was stirred at room temperature. Bromine (7.1 mL, 138 mmol) was added dropwise over 15 min via an addition funnel. The reaction mixture was then stirred at room temperature for 4 h. The clear colorless solution was diluted with water (500 mL) and extracted with dichloromethane (200 mL) three times. The combined organic layers were dried over $MgSO_4$, filtered and solvent was removed in vacuo from the filtrate to give a yellow liquid. Flash chromatography on silica gel (EtOAc:hexane::1:20) and removal of solvent from the desired combined fractions afforded a clear colorless liquid (15.4 g): $^1$H-NMR($CDCl_3$, 300 MHz): $\delta$ 7.60(d, 1H, J = 8), 6.46 (d, 1H, J = 8), 3.89 (s, 3H), 2.54 (s, 3H).

D. 6-Methoxy-2-methylpyridine-3-boronic acid.

A solution of 6-methoxy-3-bromo-2-methylpyridine (59.8 g, 296 mmol) in dry THF (429 mL) was cooled with

stirring to ~ -78 °C under a nitrogen atmosphere. A solution of n-butyl lithium (2.5 M, 130.4 mL, 326 mmol) in hexane was added dropwise over 30 min. The reaction mixture was stirred for 3 h at ~ -78 °C. A solution of tri-isopropyl borate (102.7 mL, 445 mmol) in dry THF (100 mL) was added dropwise over 30 min. The reaction mixture was warmed to ambient temperature with stirring over 16 h. Acetic acid (37.35 g, 622 mmol), then water (110 mL) were added to the reaction mixture with stirring. After 2h, the layers were separated and the organic layer was concentrated in vacuo. The residue was taken up in 2-propanol (750 mL) and solvent was removed on a rotary evaporator (bath temperature ~ 50 °C). The residue was triturated with ether. The product was collected by filtration and dried in vacuo (48.4 g) : mp > 200 °C; $^1$H-NMR($CD_3OH$, 300 MHz): δ 7.83 (d, 1H, J = 8), 6.56 (d, 1H, J = 8), 3.85 (s, 3H), 2.44 (s, 3H); GC-MS: 168 ($M^+$ + H).

E. 2-Methyl-3-(5-methylisoxazol-4-yl)-6-methoxypyridine.

A mixture of 4-iodo-5-methylisoxazole (18.2 g, 87 mmol), 6-methoxy-2-methylpyridine-3-boronic acid (14.6 g, 87 mmol), sodium bicarbonate (22.0 g, 262 mmol), water (150 mL) and DME (150 mL) was degassed three times

with stirring by the application of a vacuum and then introduction of a nitrogen atmosphere. [1,1-Bis(diphenylphosphino)ferrocene]-dichloropalladium (II) (2.14 g, 2.6 mmol) was added in one portion. The reaction mixture was degassed as before. The reaction mixture was then stirred at 80 °C for 4 h, then it was cooled to ambient temperature. Three extractions with EtOAc, drying the combined organic layers over $MgSO_4$, filtration and removal of solvent in vacuo afforded an oil. Flash chromatography (EtOAc:hexane::1:9) and removal of solvent in vacuo from the desired fractions gave the product (7.15 g): $^1$H-NMR($CDCl_3$, 300 MHz): δ 8.16 (s, 1H), 7.33 (d, 1H, J = 8), 6.63 (d, 1H, J = 8), 3.95 (s, 3H), 2.35 (s, 6H); APCI$^+$-MS: 205 ($M^+$ + H).

F. 1-Cyano-1-(2-methyl-6-methoxypyrid-3-yl)propan-2-one, sodium salt.

A mixture of sodium methoxide (25% w/w, 13 mL, 70 mmol), 2-methyl-3-(5-methylisoxazol-4-yl)-6-methoxypyridine (7.15 g, 35 mmol) and methanol (50 mL) was stirred at room temperature for 16 h. Solvent was removed in vacuo to give a yellow oil. Trituration with ether, filtration and drying in vacuo afforded the crude product as a white solid (9.3 g).

G. 5-Amino-4-(2-methyl-6-methoxypyrid-3-yl)-3-methylpyrazole.

A mixture of 1-cyano-1-(2-methyl-6-methoxypyrid-3-yl)propan-2-one, sodium salt (9.3 g), hydrazine-hydrate (6 mL, 123.3 mmol) and glacial acetic acid (150 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in 1N HCl and the resulting solution was extracted with EtOAc two times. A 1N NaOH solution was added to the aqueous layer until pH = 12. The resulting semi-solution was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to give a viscous oil (5.8 g): $^1$H-NMR ($CDCl_3$, 300 MHz): 7.37 (d, 2H, J = 8), 6.62 (d, 2H, J = 8), 3.95 (s, 3H), 2.36 (s, 3H), 2.08 (s, 3H); APCI$^+$-MS: 219 ($M^+$ + H); 260 ($M^+$ + $CH_3CN$).

H. 5-Acetamidino-4-(2-methyl-6-methoxypyrid-3-yl)-3-methylpyrazole, acetic acid salt.

Ethyl acetamidate hydrochloride (6.46g, 52.2 mmol) was added quickly to a rapidly stirred mixture of potassium carbonate (6.95g, 50.0 mol), dichloromethane (60 mL) and water (150 mL). The layers were separated and the aqueous layer was extracted with dichloromethane

(2 X 60 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed by simple distillation and the pot residue, a clear pale yellow liquid, was used without further purification.

Glacial acetic acid (1.0 mL, 17.4 mmol) was added to a stirred mixture of 5-amino-4-(2-methyl-6-methoxypyrid-3-yl)-3-methylpyrazole (3.8g, 17.4 mmol), ethyl acetamidate free base and dichloromethane (100 mL). The resulting reaction mixture was stirred at room temperature for 16 h; at the end of which time, it was concentrated in vacuo. The residue was triturated with ether, the product was filtered and washed with copious amounts of ether. The white solid was dried in vacuo (5.4 g): $^1$H-NMR ($CD_3OH$, 300 MHz): 7.43 (d, 2H, J = 8), 6.69 (d, 2H, J = 8), 4.9 (br s, 2H), 3.93 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 2.13 (s, 3H), 1.88 (s, 3H); APCI$^+$-MS: 260 ($M^+$ + H).

I. 2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-[1,3,5]-triazin-4(3H)-one.

Sodium pellets (3.9 g, 169 mmol) were added portionwise to ethanol (200 mL) with vigorous stirring. After all the sodium reacted, 5-acetamidino-4-(2-methyl-6-methoxypyrid-3-yl)-3-methylpyrazole, acetic acid salt (5.4 g, 16.9 mmol) and diethyl carbonate ( 16.4 mL, 135.3 mmol) were added. The resulting reaction mixture

was heated to reflux temperature and stirred for 18 hours. The mix was cooled to room temperature and solvent was removed in vacuo. The residue was dissolved in water and a 1N HCl solution was added slowly until pH ~ 6. The aqueous layer was extracted with EtOAc three times; the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to give a solid. Trituration with ether, filtration and drying in vacuo afforded a white solid (3.9 g): $^1$H-NMR ($CD_3OH$, 300 MHz): 7.49 (d, 2H, J = 8), 6.69 (d, 2H, J = 8), 3.93 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H); APCI$^+$-MS: 286 ($M^+$ + H).

EXAMPLE 2

Preparation of 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine

A. 4-Chloro-2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolotriazine.

A mixture of 2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 3.9 g, 13.7 mmol), di-isopropyl-ethylamine (9.5 mL, 54.7 mmol), phosphorus oxychloride (5.1 mL, 54.7 mmol) and toluene (75 mL) was stirred at reflux temperature for 4 h. The volatiles were removed in vacuo. The residue was loaded on a pad of silica gel on celite and eluted with a 1:1 mixture of EtOAc and

hexane. Solvent was removed in vacuo from the filtrate to give an oil.

B. 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

A mixture of 4-chloro-2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolotriazine, (R)-2-butylamine (2.0 mL, 20.5 mmol), di-isopropyl-ethylamine (9.5 mL, 54.7 mmol) and dry THF (25 mL) was stirred at ambient temperature for 18 hours. Solvent was removed in vacuo. Column chromatography of the residue (first using EtOAc:hexane::1:2, then using EtOAc:hexane::1:4) afforded the product. Removal of solvent in vacuo gave a white solid (2.3 g): mp = 118.3 $^{o}$C ; $^{1}$H-NMR ($CDCl_3$, 300 MHz): $\delta$ 7.41 (d, 1H, J = 8), 6.63 (d, 1H, J = 8), 6.25 (br d, 1H, J = 9), 4.35-4.30 (m, 1H), 3.95 (s, 3H), 2.49 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 1.76-1.66 (m, 2H), 1.34 (d, 3H, J = 7), 1.02 (t, 3H, J = 7); $^{13}$C-NMR ($CDCl_3$, 100.52 MHz): $\delta$ 163.8, 163.0, 155.7, 153.7, 147.8, 146.6, 141.6, 118.5, 107.4, 106.6, 53.3, 48.2, 29.7, 26.1, 22.9, 20.4, 13.1, 10.3; IR (neat, KBr, $cm^{-1}$): 3380 (m), 3371 (m), 2968 (m), 2928 (m), 2872 (w), 1621 (s), 1588 (s), 1544 (s), 1489 (s), 1460 (s), 1425 (s), 1413 (s), 1364 (s), 1346 (m), 1304 (s), 1275 (s), 1247 (s), 1198 (m), 1152 (m), 1134 (m), 1112 (m), 1034

(s), 1003 (m); ESI(+)-HRMS: Calcd for $C_{18}H_{24}N_6O$: 341.2089; Found: 341.2093 ($M^+$ + H). Anal. Calcd for $C_{18}H_{24}N_6O$: C, 63.51, H, 7.12, N, 24.69; Found: C, 63.67, H, 7.00, N, 24.49.

Utility

Rat CRF Receptor Binding Assay for the Evaluation of Biological Activity.

Receptor binding affinity to rat cortical receptors was assayed according to the published methods (E.B. De Souza, J. Neuroscience, 7: 88 (1987).

Curves of the inhibition of [$^{125}$I-Tyr$^0$]-o-CRF binding to cell membranes at various dilutions of test drug were analyzed by the iterative curve fitting program LIGAND [P.J. Munson and D. Rodbard, Anal. Biochem. 107:220 (1980), which provides Ki values for inhibition which are then used to assess biological activity.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. Synapse 1:572 (1987). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM

isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range $10^{-9}$ to $10^{-6m}$) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/$^{32}$P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 µl of [$^{3}$H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [$^{32}$P]cAMP from [$^{32}$P]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

The in vivo activity of a compound of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn Brain Research Reviews 15:71 (1990).

A compound may be tested in any species of rodent or small mammal.

A compound of this invention has utility in the treatment of imbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

A compound of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. It can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, a compound of this invention can be orally administered

daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-

coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

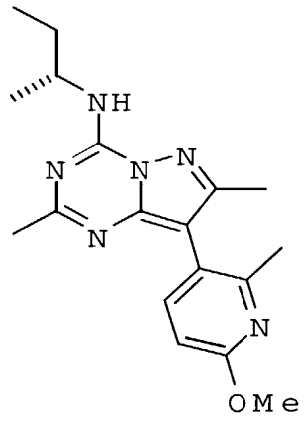
A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

What is claimed is:

1. A compound of Formula (I):




(I)

isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms.

2. A compound of claim 1, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms thereof, wherein said compound is 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

3. A compound of claim 1, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms thereof, wherein said compound is substantially free of its (S) stereoisomer.

4. A compound of claim 1, wherein said compound is 4-(2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

5. A compound of claim 1, wherein said compound is 4-((R)-2-butylamino)2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)[1,5-a]-pyrazolo-1,3,5-triazine.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 5.

8. A method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound as claimed in claim 1.

9. A method of treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal, comprising administering to the animal a therapeutically effective amount of a compound as claimed in claim 1.

10. A method for the treatment of a disorder, the treatment of which can be effected or facilitated by antagonizing CRF, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

11. A method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound as claimed in claim 5.

12. A method of treating anxiety or depression in mammals, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

13. A method of treating anxiety or depression in mammals, comprising administering to the mammal a therapeutically effective amount of a compound of claim 5.

14. A method for screening for ligands for CRF receptors, which method comprises:

a) carrying out a competitive binding assay with a CRF receptor, a compound according to claim 1 which is labelled with a detectable label, and a candidate ligand; and

b) determining the ability of said candidate ligand to displace said labelled compound.

15. A method for detecting CRF receptors in tissue comprising:

a) contacting a compound of claim 1, which is labelled with a detectable label, with a tissue, under conditions that permit binding of the compound to the tissue; and

b) detecting the labelled compound bound to the tissue.

16. A method of inhibiting the binding of CRF to a CRF-1 receptor, comprising contacting a compound of claim 1 with a solution comprising cells expressing the CRF1 receptor, wherein the compound is present in the solution at a concentration sufficient to inhibit the binding of CRF to the CRF-1 receptor.

17. An article of manufacture comprising:

a) a packaging material;

b) a compound of claim 1; and

c) a label or package insert contained within said packaging material idicating that said compound is effective for treating anxiety or depression.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/06837

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61P 25/00, 25/24; A61K 31/53; C07D 403/00

US CL : 514/245; 544/212

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/245; 544/212

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 6,191,131 B1 (HE et al.) 20 February 2001, see entire document, especially Table 7. | 1-17 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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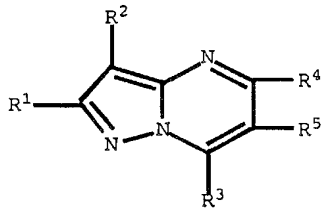


(I)

(57) Abstract

The present invention relates to pyrazolopyrimidines according to formula (I) and stereoisomers, isomers and salts thereof wherein $R^1$–$R^5$ are selected from certain alkyl, aryl and heteroaryl species as defined in the specification wherein all of the compounds are useful as CRF antagonists and are thus useful in the treatment of neurological disorders as well as a multitude of other CRF associated diseases or conditions.

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# TITLE

# PYRAZOLOPYRIMIDINES AS CRF ANTAGONISTS

## FIELD OF THE INVENTION

The present invention relates to novel compounds, compositions, and methods for the treatment of psychiatric disorders and neurological diseases, including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders, as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress. In particular, the present invention relates to novel pyrazolo[1,5-a]pyrimidines, pharmaceutical compositions containing such compounds and their use in treating psychiatric disorders, neurological diseases, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

## BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin (POMC) - derived peptide secretion from the anterior pituitary gland [J. Rivier et al., Proc. Nat. Acad. Sci. (USA) 80:4851 (1983); W. Vale et al., Science 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., Rec. Prog. Horm. Res. 39:245 (1983); G.F. Koob, Persp. Behav. Med. 2:39 (1985); E.B. De

Souza et al., J. Neurosci. 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, Physiological Reviews 69:1 (1989); J.E. Morley, Life Sci. 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, Hosp. Practice 23:59 (1988)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., Science 226:1342 (1984); C.M. Banki et al., Am. J. Psychiatry 144:873 (1987); R.D. France et al., Biol. Psychiatry 28:86 (1988); M. Arato et al., Biol Psychiatry 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., Arch. Gen. Psychiatry 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., Am J. Psychiatry 141:619 (1984); F. Holsboer et al., Psychoneuroendocrinology 9:147 (1984); P.W. Gold et al., New Eng. J. Med. 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, Arch. Gen. Psychiatry 46:1047 (1989)]. There is preliminary evidence that tricyclic antidepressants

can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., Neuropsychopharmacology 2:53 (1989)].

It has also been postulated that CRF has a role in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., Life Sci. 31:363 (1982); C.W. Berridge and A.J. Dunn Regul. Peptides 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist a-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn Horm. Behav. 21:393 (1987), Brain Research Reviews 15:71 (1990)].

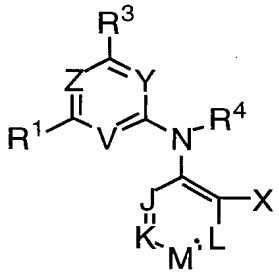
Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., Psychopharmacology 86:170 (1985); K.T. Britton et al., Psychopharmacology 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., Psychopharmacology 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., Psychopharmacology 94:306 (1988)].

It has been further postulated that CRF has a role in immunological, cardiovascular or heart-related diseases such as hypertension, tachycardia and congestive heart failure, stroke, osteoporosis, premature birth, psychosocial dwarfism, stress-induced

fever, ulcer, diarrhea, post-operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress.

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (a-helical CRF9-41) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

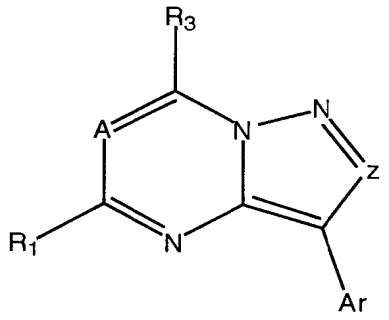
DuPont Merck PCT application US94/11050 describes corticotropin releasing factor antagonist compounds of the formula:




and their use to treat psychiatric disorders and neurological diseases. Included in the description are fused pyridines and pyrimidines of the formula:

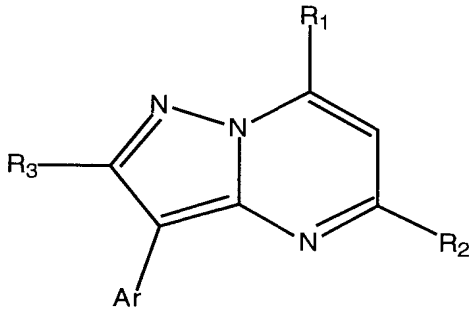
where: V is $CR^{1a}$ or N; Z is $CR^2$ or N; A is $CR^30$ or N; and D is $CR^{28}$ or N.

WO 98/03510, published in January, 1998, also describes a series of CRF antagonist compounds having the formula:



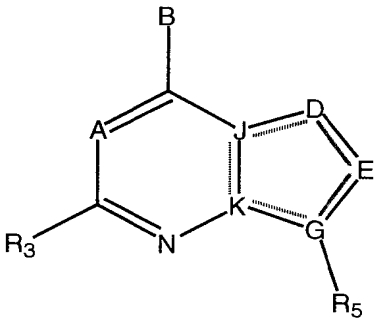

wherein z is N or $CR^2$ and A is N or CR.

WO 97/29109, published in August, 1997, similarly describes certain CRF antagonist compounds having the formula:



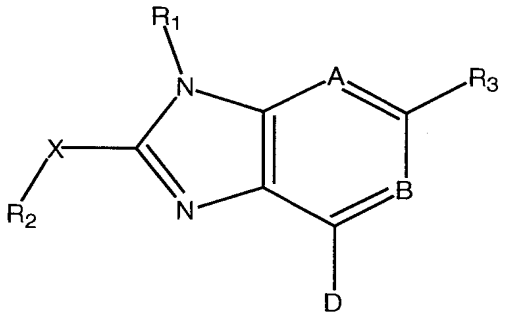

wherein Ar is phenyl, pyridyl and substituted versions thereof.

WO 98/08847, published March 5, 1998, discloses CRF antagonist compounds of the formula:



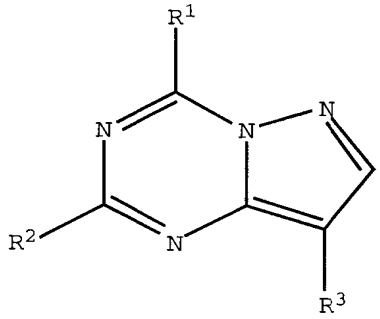
wherein B is selected from a variety of non-aryl groups and $R^5$ is selected from certain groups such as phenyl or pyridyl or substituted versions thereof.

WO 99/01454, published on January 14, 1999, discloses CRF antagonist compounds of the formula:




wherein D is an aryl or heteroaryl group and $R^1$ is selected from certain non-aryl or non-heteroaryl groups.

EP 0 269 859 (Ostuka, 1988) discloses pyrazolotriazine compounds of the formula




where $R^1$ is OH or alkanoyl, $R^2$ is H, OH, or SH, and $R^3$ is an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

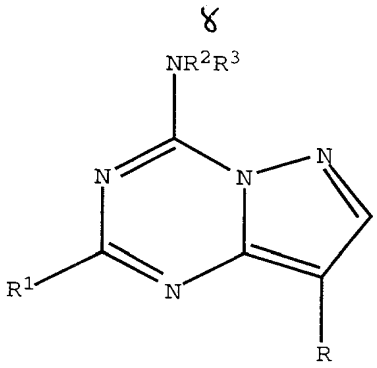
EP 0 594 149 (Ostuka, 1994) discloses pyrazolotriazine and pyrazolopyrimidine compounds of the formula

where A is CH or N, $R^0$ and $R^3$ are H or alkyl, and $R^1$ and $R^2$ are H, alkyl, alkoxyl, alkylthio, nitro, etc., and states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and prostatic carcinoma.

US 3,910,907 (ICI, 1975) discloses pyrazolotriazines of the formula:

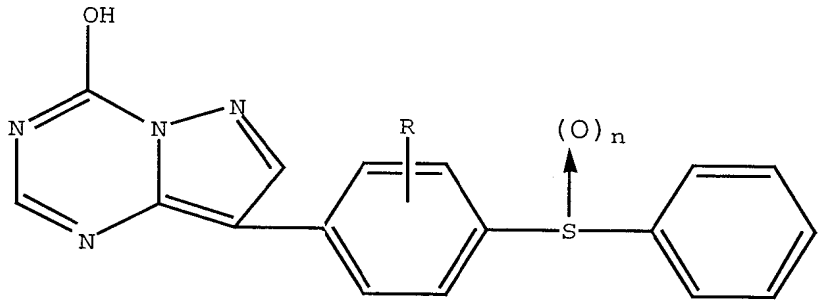
where R1 is $CH_3$, $C_2H_5$ or $C_6H_5$, X is H, $C_6H_5$, m-$CH_3C_6H_4$, CN, COOEt, Cl, I or Br, Y is H, $C_6H_5$, o-$CH_3C_6H_4$, or p-$CH_3C_6H_4$, and Z is OH, H, $CH_3$, $C_2H_5$, $C_6H_5$, n-$C_3H_7$, i-$C_3H_7$, SH, $SCH_3$, $NHC_4H_9$, or $N(C_2H_5)_2$, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

US 3,995,039 discloses pyrazolotriazines of the formula:



where $R^1$ is H or alkyl, $R^2$ is H or alkyl, $R^3$ is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

US 5,137,887 discloses pyrazolotriazines of the formula



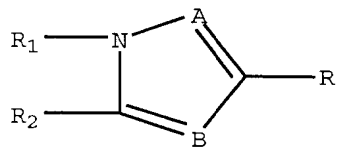
where R is lower alkoxy, and teaches that the compounds are xanthine oxidase inhibitors and are useful for treatment of gout.

US 4,892,576 discloses pyrazolotriazines of the formula

where X is O or S, Ar is a phenyl, naphthyl, pyridyl or thienyl group, $R_6$-$R_8$ are H, alkyl, etc., and $R_9$ is H,

alkyl, phenyl, etc. The patent states that the compounds are useful as herbicides and plant growth regulants.

US 5,484,760 and WO 92/10098 discloses herbicidal compositions containing, among other things, a herbicidal compound of the formula




where A can be N, B can be $CR_3$, $R_3$ can be phenyl or substituted phenyl, etc., R is $-N(R_4)SO_2R_5$ or $-SO_2N(R_6)R_7$ and $R_1$ and $R_2$ can be taken together to form

where X, Y and Z are H, alkyl, acyl, etc. and D is O or S.

US 3,910,907 and Senga et al., J. Med. Chem., 1982, 25, 243-249, disclose triazolotriazines cAMP phosphodiesterase inhibitors of the formula

where Z is H, OH, $CH_3$, $C_2H_5$, $C_6H_5$, n-$C_3H_7$, iso-$C_3H_7$, SH, $SCH_3$, NH(n-$C_4H_9$), or $N(C_2H_5)_2$, R is H or $CH_3$, and $R_1$ is $CH_3$ or $C_2H_5$. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control, male infertility, psoriasis, thrombosis, anxiety, and hypertension.

WO95/35298 (Otsuka, 1995) discloses pyrazolopyrimidines and states that they are useful as analgesics. The compounds are represented by the formula



where Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, $R^1$ is H, alkyl, etc., $R^2$ is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, $R^3$ is H, alkyl or phenyl, $R^4$ is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, $R^5$ and $R^6$ are H or alkyl.

EP 0 591 528 (Otsuka,1991) discloses anti-inflammatory use of pyrazolopyrimidines represented by the formula

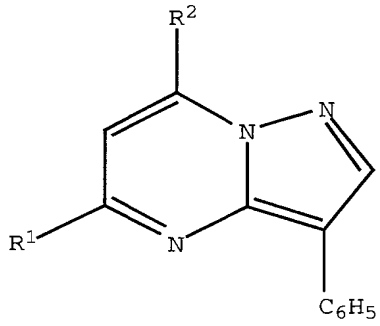


where $R_1$, $R_2$, $R_3$ and $R_4$ are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, $R_5$ is $SR_6$ or $NR_7R_8$, $R_6$ is pyridyl or optionally substituted phenyl, and $R_7$ and $R_8$ are H or optionally substituted phenyl.

Springer et al, J. Med. Chem., 1976, vol. 19, no. 2, 291-296 and Springer U.S. patents 4021,556 and 3,920,652 disclose pyrazolopyrimidines of the formula

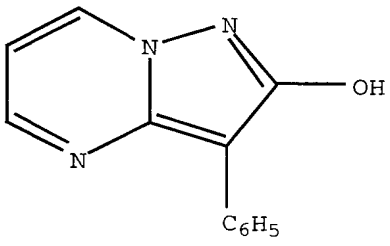
where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula




where $R^1$ is $CF_3$, $C_2F_5$, or $C_6H_4F$, and $R^2$ is $CH_3$, $C_2H_5$, $CF_3$, or $C_6H_4F$.

Maquestiau et al., Bull. Soc. Belg., vol.101, no. 2, 1992, pages 131-136 discloses a pyrazolo[1,5-a]pyrimidine of the formula



Ibrahim et al., Arch. Pharm. (weinheim) 320, 487-491 (1987) discloses pyrazolo[1,5-a]pyrimidines of the formula



where R is NH2 or OH and Ar is 4-phenyl-3-cyano-2-aminopyrid-2-yl.

Other references which disclose azolopyrimidines inclued EP 0 511 528 (Otsuka, 1992), US 4,997,940 (Dow, 1991), EP 0 374 448 (Nissan, 1990), US 4,621,556 (ICN,1997), EP 0 531 901 (Fujisawa, 1993), US 4,567,263 (BASF, 1986), EP 0 662 477 (Isagro, 1995), DE 4 243 279 (Bayer, 1994), US 5,397,774 (Upjohn, 1995), EP 0 521 622 (Upjohn, 1993), WO 94/109017 (Upjohn, 1994), J. Med. Chem., 24, 610-613 (1981), and J. Het. Chem., 22, 601 (1985) or others as additionally described herein.

## SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds which bind to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic

hypersensitivity associated with psychopathological disturbance and stress in mammals.

According to another aspect, the present invention provides novel compounds of formula (I) (described below) which are useful as antagonists of the corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds of formula (I), and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect, the present invention provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome;

stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in mammals. The preferred uses include treatment of depression and anxiety.

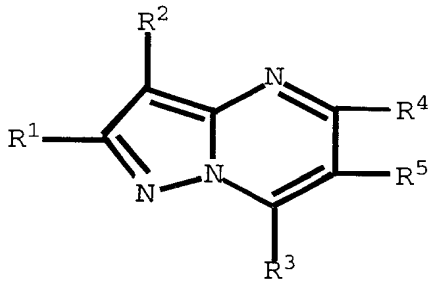
The present invention also relates to the use of a compound of formula I and other compounds generically and specifically disclosed herein in therapy.

According to a still further aspect of the invention, the compounds provided by this invention (and especially labelled compounds of this invention)

are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

## DETAILED DESCRIPTION OF INVENTION

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

$R^1$ is selected from the group consisting of

$C_{1-6}$ alkyl,
$C_{2-10}$ alkenyl,
$C_{2-10}$ alkynyl,
$C_{3-6}$ cycloalkyl,
$C_{1-6}$ alkyloxy,
$C_{1-6}$ alkylS(O)$_n$,
$-NR^{1a}R^{1B}$ wherein $R^{1a}$ and $R^{1b}$ are independently selected from H, $C_{1-4}$ alkyl, $-C(O)C_{1-4}$alkyl,
$-C(O)NR^{1a}R^{1b}$,
$-O-C(O)C_{1-4}$alkyl,

$-XR^{1c}$ wherein $R^{1c}$ is selected from H or $-C_{1-4}$ alkylaryl;
X is selected from 0 or $S(O)_n$,

wherein $R^1$ is substituted with 0-6 substituents selected from halogen, $C_{1-4}$ alkyl, $C_{1-6}$ alkyloxy, $C_{1-4}$ haloalkyl, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

$R^2$ is selected from the group consisting of
$C_{1-10}$ alkyl,
$C_{2-10}$ alkenyl,
$C_{2-10}$ alkynyl,
$C_{3-8}$ cycloalkyl,
$C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl,
$C_{1-10}$ alkyloxy,
$C_{1-10}$ alkyloxy$C_{1-10}$ alkyl,
$C_{1-4}$ alkoxy $C_{1-4}$ alkyl,
$-SO_2-C_{1-10}$alkyl
$-SO_2R^{2a}$ wherein $R^{2a}$ is aryl,
$-SO_2R^{2b}$ wherein $R^{2b}$ is heteroaryl,
$-NR^{2C}R^{2D}$ wherein $R^{2c}$ and $R^{2d}$ are independently selected from H, $C_{1-8}$ alkyl, $S(O)_nC_{1-4}$ alkyl, $C(O)NR^{2c}R^{2d}$, $CO_2C_{1-4}$alkyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $-C(O)C_{1-4}$alkyl or $R^{2c}$ and $R^{2d}$ may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,

- halogen,
-CN,
$-C(O)L$ wherein L is selected from $NR^{2c}R^{2d}$, $C_{1-6}$ alkyl, H, $-OC_{1-6}$ alkyl, $O(CH_2)_mOC_{1-6}$alkyl, $O(CH_2)_mNR^{2c}R^{2d}$, -OH, aryl, heteroaryl or $C(O)OC_{1-6}$ alkyl, wherein m is 1-3, or more particularly from,
$-C(O)NR^{2c}R^{2d}$,
$-C(O)R$ wherein R is $C_{1-6}$ alkyl,

$-C(O)OC_{1-4}$ alkyl,

$-C(O)O(CH_2)_2OR$ wherein R is $C_{1-3}$ alkyl,

$-C(O)O(CH_2)_2-NHR$ wherein R is $C_{1-3}$ alkyl,

$-C(O)O(CH_2)_2-NR^2$,

$-C(O)OH$,

$-C(O)H$,

$-C(O)Ph$,

$-C(O)R'$ wherein R' is aryl, heteroaryl or carboalkoxy;

n is 0, 1 or 2;

$R^2$ is substituted with 0-3 substituents independently selected from R', R", R"' wherein R', R" and R"' are independently selected from $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, hydroxy$C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{1-6}$ alkyloxy, hydroxy, or

$R^2$ is substituted with 0-3 substituents independently selected from:

halogen,

$-CN$,

$-S(O)_nR^{2e}$ wherein $R^{2e}$ is selected from $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl;

$-COR^{2f}$ wherein $R^{2f}$ is selected from H, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, and $C_{3-6}$ cycloalkyl$C_{1-4}$ alkyl;

$-CO_2R^{2f}$,

$-NR^{2g}COR^{2f}$ wherein $R^{2g}$ is selected from H, $C_{1-6}$ alkyl, $C_{3-7}$ c-alkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, wherein $R^{2h}$ is selected from H, $C_{1-6}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl and $C_{3-6}$ cycloalkyl$C_{1-6}$ alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

$C_{3-8}$ cycloalkyl wherein 0-1 carbon atoms in the $C_{4-8}$ cycloalkyl is replaced by a group selected from -O-, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$, and $-NSO_2R^{2e}$; and wherein $N_4$ in 1-piperazinyl is substituted with 0-1 substituents selected from $R^{2g}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$; or

the group $R^{2i}$, $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{2l}$ and in wich 0-1 carbons of $C_{4-8}$ cycloalkyl is replaced by -O-, wherein

$R^{2i}$ is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl, each $R^{2i}$ being substituted with 0-1 $OR^{2m}$ and 0-5 substituents independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2n}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$;

$R^{2j}$ is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted on any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$;

$R^{2k}$ is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for $R^{2j}$, each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group $R^{2f}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$;

wherein

$R^{2l}$ is H, $C_{1-4}$ alkyl, $C_{3-6}$ cycloalky-$C_{1-4}$ alkyl and $C_{3-8}$ cycloalkyl;

$R^{2m}$ is H, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl, $C_{1-2}$ alkyloxy $C_{1-2}$ alkyl, $C_{1-4}$ haloalkyl, $R^{2q}S(0)_n-C_{1-4}$ alkyl and $R^{2r}R^{2s}N-C_{2-4}$ alkyl;

$R^{2n}$ is H, $C_{1-6}$ alkyl, $C_{3-10}$ cyloalkyl, $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkyl, $C_{1-2}$ alkyloxy $C_{1-2}$ alkyl, and $C_{1-4}$ haloalkyl;

$R^{2o}$ and $R^{2p}$ are independently selected at each occurrence from H, $C_{1-6}$ alkyl, $C_{3-10}$ cycloalkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl and $C_{1-4}$ haloalkyl;

$R^{2q}$ is selected from $C_{1-6}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{3-6}$ cycloalkyl- $C_{1-6}$ alkyl, aryl, aryl($C_{1-4}$ alkyl), heteroaryl and heleroaryl ($C_{1-4}$ alkyl)- and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group $C_{1-4}$ alkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy $C_{1-4}$ haloalkoxy, and dimethylamino;

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein $N_4$ in 1-piperiazinyl is substituted with 0-1 substituents selected from the group $R^{2t}$, $CO_2R^{2q}$, $COR^{2q}$ and $SO_2R^{2q}$;

$R^{2t}$ is selected from H, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy -$C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{3-6}$ cycloalkyl - $C_{1-6}$ alkyl, aryl, aryl ($C_{1-4}$ alkyl)-, heteroaryl and heteroaryl ($C_{1-4}$ alkyl);

$R^3$ is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, methylenedioxy, $C_{1-4}$ alkyloxy-$C_{1-4}$ alkyloxy, $-OR^{2m}$, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, $-NO_2$, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy, Br, Cl, F, I, -CN, dimethylamino, $CF_3$, $C_2F_5$, $OCF_3$, $SO_2Me$ and acetyl;

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substitued at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, F, I, $C_{1-4}$ haloalkyl, -CN, $NR^{2g}R^{2h}$, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, $COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{3a}$, $COR^{3a}$ and $SO_2R^{3a}$ wherein,

$R^{3a}$ is selected from the group $C_{1-6}$ alkyl, $C_{1-4}$ cycloalkyl-$C_{1-6}$ alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group

$C_{1-4}$ alkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy, $C_{1-4}$ haloalkoxy, and dimethylamino;

$R^4$ and $R^5$ are independently selected at each occurrence from H, Br, Cl, F, I, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyloxy, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylsulfinyl, $C_{1-6}$ alkylsulfonyl, amino, $C_{1-4}$ alkylamino, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of $C_{1-7}$ alkyl, $C_{3-8}$ cycloalkyl, Br, Cl, F, I, -C(O)H, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy, $C_{1-4}$ haloalkoxy, $C_{1-4}$ alkylthio, $C_{1-4}$ alkylsulfinyl, $C_{1-4}$ alkylsulfonyl, $C_{1-6}$ alkylamino and $(C_{1-4}$ alkyl$)_2$ amino and wherein $R^4$ and $R^5$ non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, $-OC_{1-6}$-alkyl and $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{3-7}$ c-alkyl, $C_{1-6}$ alkyl$(OH)_nCO_2R$ wherein R is H or $C_{1-6}$ alkyl, $C_{1-6}$ alkyl$(OH)_n$ ,wherein n is 0-3 or $R^4$ and $R^5$ may join together to form a $C_{3-6}$ alkylene chain; with the proviso that the compounds of Formula I with $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ as specifically defined below are excluded:

(a) a compound of formula I wherein $R^1$ is unsubstituted, unbranched (linear) $C_{1-3}$ alkyl and $R^2$ is -C(O)-Ph (EP O 129 847 A2, US 4,521,422, US 4,654,347);

(b) a compound of formula I, wherein $R^5$ is H or $C_{1-3}$ alkyl and $R^3$ is pyridyl, pyridyl-N-oxide, thien-3-yl or furan-3-yl or $C_{1-3}$ alkyl substituted versions thereof and $R^1$ is carboamoyl or unsubstituted, unbranched $C_{1-3}$ alkyl, $R^2$ is F, Cl, Br, formyl, carboxyl, CN, hydroxymethyl, unsubstituted, unbranched $C_{1-3}$ alkyl, -C(O)R, -C(O)OR, $-CH_2OR$, $-C(O)O(CH_2)_2OR$, $-C(O)O(CH_2)_2NHR$, or $-C(O)O(CH_2)_2NR^2$ wherein R is $C_{1-3}$ alkyl (US 4,281,000);

(c) a compound of formula I, wherein $R^1$ is unsubstituted, unbranched $C_{1-3}$ alkyl and $R^2$ is halogen, CN or -C(O)R wherein R is H, $C_{1-3}$ alkyl or $C_{1-4}$ alkoxy, $R^3$ is Ph substituted with $NR^{2g}C(O)R^{2m}$ (US 4,626,538)

(d) a compound of formula I, $R^2$ is CN, halogen, $CO_2R$ with R equal to $C_{1-3}$ alkyl, unsubstituted, unbranched $C_{1-3}$ alkyl, $C_{1-3}$ haloalkyl or $CONH_2$ and $R^1$ is equal to OR, SR wherein R is $C_{1-3}$ alkyl, $C_{1-4}$ haloalkyl or $C_{3-4}$ halocycloalkyl, and $R^3$ is phenyl or substituted phenyl (US 5,127,936);

(e) a compound of formula I, wherein $R^5$ is H or $C_{1-3}$ alkyl; $R^3$ is phenyl, ortho-trifluoromethylphenyl, meta-trifluorophenyl or meta-methoxyphenyl; $R^1$ is carbamoyl or unsubstituted $C_{1-3}$ alkyl; $R^2$ is halogen, formyl, carboxyl, cyano, hydroxymethyl, unsubstituted, unbranched $C_{1-3}$ alkyl, -C(O)R, -C(O)OR, $CH_2OR$, $-C(O)O(CH_2)_2OR$, $-C(O)O(CH_2)_2NHR$ or $-C(O)O(CH_2)_2NR^2$ wherein R is $C_{1-3}$ alkyl (US 4,178,449);

(f) no entry

(g) in a compound of formula I, $R^2$ is CN, $R^1$ is methyl, $R^4$ and $R^5$ are H, $R^3$ is phenyl substituted with imidazo (or 2-methylimidazo) through the imidazo nitrogen atom (Registry Reference 20, 21);

(h) in a compound of formula I, $R^2$ is CN, $R^1$ is $SCH_3$, $R^3$ is para-chlorophenyl, $R^4$ is $SCH_3$ and $R^5$ is H (registry reference 25);

(i) in a compound of formula I, $R^2$ is CN, $R^1$ is $SCH_3$, $R^3$ is pyrid-4-yl, $R^4$ is $SCH_3$ and $R^5$ is H (Registry Reference 26);

(j) in a compound of formula I, $R^2$ is CN, $R^1$ is $SCH_3$, $R^3$ is Ph, $R^4$ is $SCH_3$ and $R^5$ is H (Registry Reference 27);

(k) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $SCH_3$, $R^3$ is pyrid-3-yl, $R^4$ is $SCH_3$ and $R^5$ is H (Registry Reference 28);

(l) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $SCH_3$, $R^3$ is Ph, $R^4$ is $SCH_3$ (or Ph) and $R^5$ is H (Registry Reference 29, 31);

(m) in a compound of formula I, $R^2$ is C(O)OEt, $R^1$ is $SCH_3$, $R^3$ is Ph, $R^4$ is $SCH_3$ (or Ph) and $R^5$ is H (registry reference 30, 32);

(n) in a compound of formula I, $R^1$ is $N(C(O)CH_3)_2$, $R^2$ is $CH_2Ph$(p-Me, p-Cl), $R^3$ is Ph (p-ClPh), $R^4$ is $SCH_3$ and $R^5$ is H (Registry Reference 33, 34);

(o) in a compound of formula I, $R^1$ is $N(C(O)CH_3)_2$, $R^2$ is $CH_2Ph$(p-OMe), $R^3$ is p-ClPh, $R^4$ is $SCH_3$ and $R^5$ is H (registry ref. 35);

(p) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is Ph, $R^4$ is H and $R^5$ is H (registry ref. 44);

(q) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $CH_3$, $R^3$ is Ph, $R^4$ is $CH_3$ and $R^5$ is H (reg. ref. 45);

(s) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $CH_3$, $R^3$ is pyrid-4-yl, $R^4$ and $R^5$ are H (reg. ref. 46);

(t) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $CH_3$, $R^3$ is m-$CF_3$Ph, $R^4$ and $R^5$ are H (reg. ref. 47);

(u) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is Ph, $R^4$ is $CH_3$ and $R^5$ is H (reg. ref. 48);

(v) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is pyrid-4-yl, $R^4$ and $R^5$ are H (reg. ref. 49);

(w) no entry

(x) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)O$-iPr (reg. ref. 75);

(y) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)O$-nPr (reg. ref. 76);

(z) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)OMe$ (reg. ref. 77);

(aa) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)OH$ (reg. ref. 78);

(bb) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is $-CH_2OH$ (reg. ref. 100);

(cc) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is -C(O)H (reg. ref. 105);

(dd) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is -CH=CH-C(O)H (reg. ref. 110);

(ee) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)OEt$ (reg. ref. 115);

(ff) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)O^-Na^+$ (reg. ref. 120);

(gg) in a compound of formula I, $R^2$ is CN, $R^1$ is $CF_3$, $R^3$ is m-Cl-Ph, $R^4$ is $CH_3$ and $R^5$ is H (reg. ref. 130);

(hh) in a compound of formula I, $R^2$ is CN, $R^1$ is $CF_3$, $R^3$ is m-$CF_3$-Ph, $R^4$ is $CH_3$ and $R^5$ is H (reg. ref. 132);

(ii) in a compound of formula I, $R^2$ is CN, $R^1$ is $CF_3$, $R^3$ is Ph, $R^4$ is $CH_3$ and $R^5$ is H (reg. ref. 133);

(jj)-(mm) no entry

(nn) in a compound of formula I, $R^2$ is $-C(O)NH_2$, $R^1$ is Me, $R^3$ is Ph, $R^4$ is H and $R^5$ is Me (reg. ref. 140);

(oo) in a compound of formula I, $R^2$ is CN, $R^1$ is Me, $R^3$ is Ph, $R^4$ is H and $R^5$ is Me (reg. ref. 141);

(pp) in a compound of formula I, $R^2$ is CN, $R^1$ is Me, $R^3$ is o-Cl,m-Cl-Ph, $R^4$ is H and $R^5$ is H (reg. ref. 144);

(qq) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $CH_3$, $R^3$ is Ph, $R^4$ and $R^5$ are H (reg. ref. 145);

(rr) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $CH_3$, $R^3$ is 0-CL,m-Cl-Ph, $R^4$ and $R^5$ are H (reg. ref. 146);

(ss) in a compound of formula I, $R^2$ is C(O)OMe, $R^1$ is $-SCH_2$-Ph, $R^3$ is Ph, $R^4$ is Me and $R^5$ is H (reg. ref. 147);

(tt) in a compound of formula I, $R^2$ is C(O)OMe, $R^1$ is $-SCH_2$-Ph, $R^3$ is Ph, $R^4$ is H and $R^5$ is H (reg. ref. 148);

(uu) in a compound of formula I, $R^2$ is C(O)Ph, $R^1$ is Me, $R^3$ is pyrid-4-yl, $R^4$ and $R^5$ are H (reg. ref. 154);

(vv) in a compound of formula I, $R^2$ is C(O)Ph, $R^1$ is Me, $R^3$ is m-$CF_3$-Ph, $R^4$ and $R^5$ are H (reg. ref. 155);

(ww) in a compound of formula I, $R^2$ is C(O)Ph, $R^1$ is Me, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H (reg. ref. 156);

(xx) in a compound of formula I, $R^2$ is CN, $R^1$ is $SCH_3$, $R^3$ is Ph, $R^4$ is Ph and $R^5$ is H (reg. ref. 157);

(yy) in a compound of formula I, $R^2$ is CN, $R^1$ is $SCH_3$, $R^3$ is Ph, $R^4$ is Ph and $R^5$ is H (reg. ref. 157);

(zz) in a compound of formula I, $R^2$ is Cl, $R^1$ is Et, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H (reg. ref. 163);

(aaa) in a compound of formula I, $R^2$ is $CO_2H$, $R^1$ is Et, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H (reg. ref. 164);

(bbb) in a compound of formula I, $R^2$ is $CO_2H$, $R^1$ is $CH_3$, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H and H Cl salt (reg. ref. 165);

(ccc) in a compound of formula I, $R^2$ is C(O)OEt, $R^1$ is $CH_3$, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H (reg. ref. 166);

(ddd) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is pyrid-3-yl, $R^4$ is H and $R^5$ is $CH_3$ (reg. ref. 167);

(eee) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H (reg. ref. 168);

(fff) in a compound of formula I, $R^2$ is C(O)OEt, $R^1$ is Et, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H (reg. ref. 169);

(ggg) in a compound of formula I, $R^2$ is CN, $R^1$ is Et, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H (reg. ref. 170);

(hhh) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is m-$CF_3$Ph, $R^4$ and $R^5$ are H (reg. ref. 172);

(iii) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_2CN$, $R^3$ is m-$CF_3$-Ph, $R^4$ and $R^5$ are H (reg. ref. 173);

(jjj) in a compound of formula I, $R^2$ is C(O)OMe, $R^1$ is Me, $R^3$ is m-$CF_3$-Ph, $R^4$ and $R^5$ are H (reg. ref. 174);

(kkk) in a compound of formula I, $R^2$ is CN, $R^1$ is Et, $R^3$ is m-OMe-Ph, $R^4$ and $R^5$ are H (reg. ref. 175);

(lll) in a compound of formula I, $R^2$ is C(O)OEt, $R^1$ is Et, $R^3$ is Ph, $R^4$ and $R^5$ are H (reg. ref. 176);

(mmm) in a compound of formula I, $R^2$ is C(O)OEt, $R^1$ is Et, $R^3$ is m-$CF_3$-Ph, $R^4$ and $R^5$ are H (reg. ref. 177);

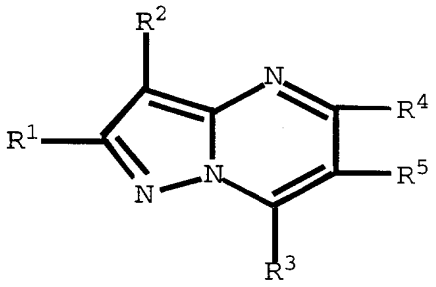
(nnn) in a compound of formula I, $R^2$ is CN, $R^1$ is Et, $R^3$ is m-$CF_3$-Ph, $R^4$ is H and $R^5$ is $CH_3$ (reg. ref. 178);

(ooo) in a compound of formula I, $R^2$ is CN, $R^1$ is Et, $R^3$ is m-$CF_3$, $R^4$ and $R^5$ are H (reg. ref. 179);

(ppp) in a compound of formula I, $R^2$ is CN, $R^1$ is $C(O)NH_2$, $R^3$ is m-$CF_3$-Ph, $R^4$ and $R^5$ are H (reg. ref. 180);

(qqq) in a compound of formula I, $R^2$ is CN, $R^1$ is Et, $R^3$ is Ph, $R^4$ and $R^5$ are H (reg. ref. 181).

[1'] In a preferred embodiment, the present invention provides a novel compound of formula I:




(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

$R^1$ is selected from the group consisting of

$C_{1-6}$ alkyl,
$C_{2-10}$ alkenyl,
$C_{2-10}$ alkynyl,
$C_{3-6}$ cycloalkyl,
$C_{1-6}$ alkyloxy,
$C_{1-6}$ alkyl$S(O)_n$,
$-NR^{1a}R^{1B}$ wherein $R^{1a}$ and $R^{1b}$ are independently selected from H, $C_{1-4}$ alkyl, $-C(O)C_{1-4}$alkyl,
$-C(O)NR^{1a}R^{1b}$,
$-O-C(O)C_{1-4}$alkyl,

$-XR^{1c}$ wherein $R^{1c}$ is selected from H or $-C_{1-4}$ alkylaryl;
X is selected from 0 or $S(O)_n$,

wherein $R^1$ is substituted with 0-6 substituents selected from halogen, $C_{1-4}$ alkyl, $C_{1-6}$ alkyloxy, $C_{1-4}$ haloalkyl, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

$R^2$ is selected from the group consisting of
$C_{1-10}$ alkyl excluding unsubstituted, unbranched $C_{1-3}$alkyl,
$C_{2-10}$ alkenyl,
$C_{2-10}$ alkynyl,
$C_{3-8}$ cycloalkyl,
$C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl,
$C_{1-10}$ alkyloxy,
$C_{1-10}$ alkyloxy$C_{1-10}$ alkyl,
$C_{1-4}$ alkoxy $C_{1-4}$ alkyl,

$-SO_2-C_{1-10}$alkyl

$-SO_2R^{2a}$ wherein $R^{2a}$ is aryl,

$-SO_2R^{2b}$ wherein $R^{2b}$ is heteroaryl,

$-NR^{2C}R^{2D}$ wherein $R^{2c}$ and $R^{2d}$ are independently selected from H, $C_{1-8}$ alkyl, $S(O)_nC_{1-4}$ alkyl, $C(O)NR^{2c}R^{2d}$, $CO_2C_{1-4}$alkyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $-C(O)C_{1-4}$alkyl or $R^{2c}$ and $R^{2d}$ may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,

n is 0, 1 or 2;

$R^2$ is substituted with 0-3 substituents independently selected from R', R", R"' wherein R', R" and R"' are independently selected from $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, hydroxy$C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{1-6}$ alkyloxy, hydroxy, or

$R^2$ is substituted with 0-3 substituents independently selected from:

-CN,

$-S(O)_nR^{2e}$ wherein $R^{2e}$ is selected from $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl;

$-COR^{2f}$ wherein $R^{2f}$ is selected from H, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, and $C_{3-6}$ cycloalkyl$C_{1-4}$ alkyl;

$-CO_2R^{2f}$,

$-NR^{2g}COR^{2f}$ wherein $R^{2g}$ is selected from H, $C_{1-6}$ alkyl, $C_{3-7}$ c-alkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, wherein $R^{2h}$ is selected from H, $C_{1-6}$ alkyl,

$C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl and $C_{3-6}$ cycloalkyl$C_{1-6}$ alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

$C_{3-8}$ cycloalkyl wherein 0-1 carbon atoms in the $C_{4-8}$ cycloalkyl is replaced by a group selected from $-O-$, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$, and $-NSO_2R^{2e}$; and wherein $N_4$ in 1-piperazinyl is substituted with 0-1 substituents selected from $R^{2g}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$; or

the group $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{2i}$ and in wich 0-1 carbons of $C_{4-8}$ cycloalkyl is replaced by $-O-$, wherein

$R^{2j}$ is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl

and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted on any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$;

$R^{2k}$ is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for $R^{2j}$, each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group $R^{2f}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$;

wherein

$R^{21}$ is H, $C_{1-4}$ alkyl, $C_{3-6}$ cycloalky-$C_{1-4}$ alkyl and $C_{3-8}$ cycloalkyl;

$R^{2m}$ is H, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl, $C_{1-2}$ alkyloxy $C_{1-2}$ alkyl, $C_{1-4}$ haloalkyl, $R^{2q}S(0)_n$-$C_{1-4}$ alkyl and $R^{2r}R^{2s}N$-$C_{2-4}$ alkyl;

$R^{2n}$ is H, $C_{1-6}$ alkyl, $C_{3-10}$ cyloalkyl, $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkyl, $C_{1-2}$ alkyloxy $C_{1-2}$ alkyl, and $C_{1-4}$ haloalkyl;

$R^{2o}$ and $R^{2p}$ are independently selected at each occurrence from H, $C_{1-6}$ alkyl, $C_{3-10}$ cycloalkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl and $C_{1-4}$ haloalkyl;

$R^{2q}$ is selected from $C_{1-6}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{3-6}$ cycloalkyl- $C_{1-6}$ alkyl, aryl, aryl($C_{1-4}$ alkyl), heteroaryl and heleroaryl ($C_{1-4}$ alkyl)- and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group $C_{1-4}$ alkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy $C_{1-4}$ haloalkoxy, and dimethylamino;

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein $N_4$ in 1-piperiazinyl is substituted with 0-1 substituents selected from the group $R^{2t}$, $CO_2R^{2q}$, $COR^{2q}$ and $SO_2R^{2q}$;

$R^{2t}$ is selected from H, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy $-C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{3-6}$ cycloalkyl - $C_{1-6}$ alkyl, aryl, aryl ($C_{1-4}$ alkyl)-, heteroaryl and heteroaryl ($C_{1-4}$ alkyl);

$R^3$ is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, methylenedioxy, $C_{1-4}$ alkyloxy-$C_{1-4}$ alkyloxy, $-OR^{2m}$, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, $-NO_2$, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being

substituted with 0-4 substituents selected from the group $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy, Br, Cl, F, I, -CN, dimethylamino, $CF_3$, $C_2F_5$, $OCF_3$, $SO_2Me$ and acetyl;

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substitued at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, F, I, $C_{1-4}$ haloalkyl, -CN, $NR^{2g}R^{2h}$, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, $COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{3a}$, $COR^{3a}$ and $SO_2R^{3a}$ wherein,

$R^{3a}$ is selected from the group $C_{1-6}$ alkyl, $C_{1-4}$ cycloalkyl-$C_{1-6}$ alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group $C_{1-4}$ alkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy, $C_{1-4}$ haloalkoxy, and dimethylamino;

$R^4$ and $R^5$ are independently selected at each occurrence from H, Br, Cl, F, I, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyloxy, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylsulfinyl, $C_{1-6}$ alkylsulfonyl, amino, $C_{1-4}$ alkylamino, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of $C_{1-7}$

alkyl, $C_{3-8}$ cycloalkyl, Br, Cl, F, I, -C(O)H, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy, $C_{1-4}$ haloalkoxy, $C_{1-4}$ alkylthio, $C_{1-4}$ alkylsulfinyl, $C_{1-4}$ alkylsulfonyl, $C_{1-6}$ alkylamino and $(C_{1-4}$ alkyl$)_2$ amino and wherein $R^4$ and $R^5$ non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, $-OC_{1-6}$-alkyl and $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{3-7}$ c-alkyl, $C_{1-6}$ alkyl$(OH)_nCO_2R$ wherein R is H or $C_{1-6}$ alkyl, $C_{1-6}$ alkyl$(OH)_n$ ,wherein n is 0-3 or $R^4$ and $R^5$ may join together to form a $C_{3-6}$ alkylene chain.

[2] The present invention relates to a compound as described directly above in [1] or [1'] wherein

$R^1$ is selected from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, $-XR^{1c}$ wherein $R^1$ is substituted with 0-6 substituents selected from halogen, $C_{1-4}$ alkyl or $C_{1-4}$ haloalkyl;

$R^2$ is selected from substituted-$C_{1-10}$ alkyl, branched $C_{3-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, $C_{3-8}$ cycloalkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl, $-NR^{2c}R^{2d}$ wherein, in the case of substituted-$C_{1-10}$ alkyl, 1-3 substitutents are independently selected from the group $R^{2i}$, $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{21}$ and in wich 0-1 carbons of $C_{4-8}$ cycloalkyl is replaced by -O- and wherein the $R^2$ groups, other than substituted-$C_{1-10}$ alkyl, are substituted with 0-3 substituents independently selected from the group $R^{2i}$, $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{21}$ and in wich 0-1 carbons of $C_{4-8}$ cycloalkyl is replaced by -O-.

[3] The present invention also relates to a compound described in groups [1], [1'] or [2] wherein $R^3$ is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

[4] The present invention relates to a compound described directly above in groups [1'] and [1]-[3] wherein $R^3$ is substituted with 0-4 substituents independently selected from halogen, $C_{1-4}$ alkyloxy, $C_{1-6}$ alkyl or NR'R" wherein R' and R" are independently selected from H or $C_{1-6}$ alkyl.

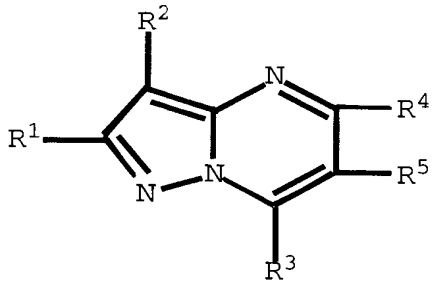
[5] The present invention preferrably relates to a compound as described directly above in groups [1'] and [1]-[4] wherein $R^3$ is selected from 2,4-dichlorophenyl, 2-chloro-4-methoxyphenyl, 2,4,6-trimethylphenyl, 2,4,6-trimethoxyphenyl, 2-dimethylamino-4-methyl-pyridin-5-yl, 2,4-dichloro-5-fluorophenyl, 2-chloro-4-methoxy-5-fluorophenyl, 2-chloro-4,5-dimethoxyphenyl or 2-chloro-4,5-dimethoxyphenyl.

[6] The present invention also preferrably relates to a compound as described in groups [1'] and [2]-[5] wherein $R^2$ is selected from $C_1$ alkyl of the formula -CR'R"R"' wherein R', R" and R"' are independently selected from H, $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, hydroxy$C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{1-6}$ alkyloxy, hydroxy, with the proviso that each of R',R" and R'" cannot be H;

or $R^2$ is selected from $NR^{2c}R^{2d}$ wherein $R^{2c}$ and $R^{2d}$ are independently selected from H or $C_{1-6}$ alkyl.

[7] The present invention preferrably relates to a compound according to groups [1'] and [1]-[6] wherein $R^3$ is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom wherein, aryl is phenyl, each phenyl being substituted with 0-5 substituents independently selected at each occurrence from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, methylenedioxy, $C_{1-4}$ alkyloxy-$C_{1-4}$ alkyloxy, $-OR^{2m}$, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy, Br, Cl, F, I, -CN, dimethylamino, $CF_3$, $C_2F_5$, $OCF_3$, $SO_2Me$ and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substitued at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, $COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each pyridyl being substituted at any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{3a}$, $COR^{3a}$ and $SO_2R^{3a}$ .

[8] The present invention preferrably relates to a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein

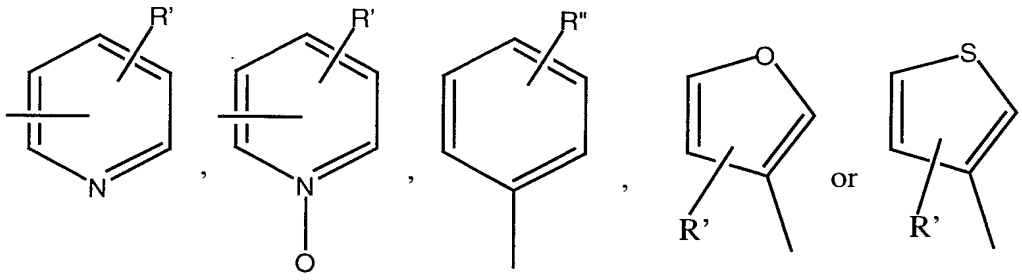
$R^1$ is selected from $C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy, -SH or OH;

$R^2$ is selected from $C_{1-4}$ alkyl which is unsubstituted or substituted with 1-4 substitutents selected from $C_{1-6}$ alkyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyl$OR^{2g}$, $C_{2-6}$ alkenyl or $OR^{2g}$ wherein $R^{2g}$ is H or $C_{1-6}$ alkyl;

$R^3$ is selected from an aryl or heteroaryl group bonded through an unsaturated carbon atom that is unsubstituted or substituted with 1-4 substituents selected from Cl, F, I, Br, -OH, $CF_3$, $S(O)_nC_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $C_{1-6}$ alkyl or $NR^{2g}R^{2h}$ wherein $R^{2g}$ and $R^{2h}$ are independently selected from H or $C_{1-6}$ alkyl;

$R^4$ and $R^5$ are independently selected from H, $C_{1-6}$ alkyl or $C_{1-6}$ alkyloxy,

with the proviso that when $R^1$ and $R^2$ are unsubstituted, unbranched $C_{1-3}$ alkyl, $R^3$ may not be




wherein R' is H or $C_{1-3}$ alkyl and R" is H or o-trifluoromethyl, m-trifluoromethyl or m-methoxy (see 4,281,000).

[9] The present invention also relates to a compound according to group [8] wherein $R^3$ is substituted with 2-4 substituents.

[10] The present invention also relates to a compound according to group [8] or[9] wherein $R^2$ is substituted with 1-4 substituents.

[11] The present invention also relates to a compound according to groups [8]-[10] having the formulae shown in Table 1.

[12] The present invention also relates to a method of antagonizing a CRF-1 receptor in mammals including humans wherein binding to the receptor causes and ultimately results in the treatment of affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms,

inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of Formula (I) wherein

$R^1$ is selected from the group consisting of

$C_{1-6}$ alkyl,

$C_{2-10}$ alkenyl,

$C_{2-10}$ alkynyl,

$C_{3-6}$ cycloalkyl,

$C_{1-6}$ alkyloxy,

$C_{1-6}$ alkyl$S(O)_n$,

$-NR^{1a}R^{1B}$ wherein $R^{1a}$ and $R^{1b}$ are independently selected from H, $C_{1-4}$ alkyl, $-C(O)C_{1-4}$alkyl, $-C(O)NR^{1a}R^{1b}$, $-O-C(O)C_{1-4}$alkyl,

$-XR^{1c}$ wherein $R^{1c}$ is selected from H or $-C_{1-4}$ alkylaryl;
X is selected from 0 or $S(O)_n$,

wherein $R^1$ is substituted with 0-6 substituents selected from halogen, $C_{1-4}$ alkyl, $C_{1-6}$ alkyloxy, $C_{1-4}$ haloalkyl, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

$R^2$ is selected from the group consisting of

$C_{1-10}$ alkyl,

$C_{2-10}$ alkenyl,

$C_{2-10}$ alkynyl,

$C_{3-8}$ cycloalkyl,

$C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl,

$C_{1-10}$ alkyloxy,

$C_{1-10}$ alkyloxy$C_{1-10}$ alkyl,

$C_{1-4}$ alkoxy $C_{1-4}$ alkyl,

$-SO_2-C_{1-10}$alkyl

$-SO_2R^{2a}$ wherein $R^{2a}$ is aryl,

$-SO_2R^{2b}$ wherein $R^{2b}$ is heteroaryl,

$-NR^{2C}R^{2D}$ wherein $R^{2c}$ and $R^{2d}$ are independently selected from H, $C_{1-8}$ alkyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $-C(O)C_{1-4}$alkyl or $R^{2c}$ and $R^{2d}$ may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,

- halogen,

-CN,

$-C(O)NR^{2c}R^{2d}$,

-C(O)R wherein R is $C_{1-6}$ alkyl,

$-C(O)OC_{1-4}$ alkyl,

$-C(O)O(CH_2)_2OR$ wherein R is $C_{1-3}$ alkyl,

$-C(O)O(CH_2)_2$-NHR wherein R is $C_{1-3}$ alkyl,

$-C(O)O(CH_2)_2-NR^2$,

-C(O)OH,

-C(O)H,

-C(O)Ph,

-C(O)R' wherein R' is aryl, heteroaryl or carboalkoxy;

n is 0, 1 or 2;

$R^2$ is substituted with 0-3 substituents independently

selected from R', R", R"' wherein R', R" and R"' are independently selected from $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, hydroxy$C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{1-6}$ alkyloxy, hydroxy, or

$R^2$ is substituted with 0-3 substituents independently selected from

halogen,

-CN,

$-S(O)_nR^{2e}$ wherein $R^{2e}$ is selected from $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl;

$-COR^{2f}$ wherein $R^{2f}$ is selected from H, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, and $C_{3-6}$ cycloalkyl$C_{1-4}$ alkyl;

$-CO_2R^{2f}$,

$-NR^{2g}COR^{2f}$ wherein $R^{2g}$ is selected from H, $C_{1-6}$ alkyl, $C_{3-7}$ c-alkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, wherein $R^{2h}$ is selected from H, $C_{1-6}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl and $C_{3-6}$ cycloalkyl$C_{1-6}$ alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

$C_{3-8}$ cycloalkyl wherein 0-1 carbon atoms in the $C_{4-8}$ cycloalkyl is replaced by a group selected from

-O-, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$,

and $-NSO_2R^{2e}$; and wherein $N_4$ in

1-piperazinyl is substituted with 0-1 substituents selected from $R^{2g}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$; or

the group $R^{2i}$, $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{2l}$ and in wich 0-1 carbons of $C_{4-8}$ cycloalkyl is replaced by -O-, wherein

$R^{2i}$ is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl, each $R^{2i}$ being substituted with 0-1 $OR^{2m}$ and 0-5 substituents independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2n}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$;

$R^{2j}$ is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted

on any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$;

$R^{2k}$ is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for $R^{2j}$, each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group $R^{2f}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$;

wherein

$R^{2l}$ is H, $C_{1-4}$ alkyl, $C_{3-6}$ cycloalky-$C_{1-4}$ alkyl and $C_{3-8}$ cycloalkyl;

$R^{2m}$ is H, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl, $C_{1-2}$ alkyloxy $C_{1-2}$ alkyl, $C_{1-4}$ haloalkyl, $R^{2q}S(0)_n$-$C_{1-4}$ alkyl and $R^{2r}R^{2s}N$-$C_{2-4}$ alkyl;

$R^{2n}$ is H, $C_{1-6}$ alkyl, $C_{3-10}$ cyloalkyl, $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkyl, $C_{1-2}$ alkyloxy $C_{1-2}$ alkyl, and $C_{1-4}$ haloalkyl;

$R^{2o}$ and $R^{2p}$ are independently selected at each occurrence from H, $C_{1-6}$ alkyl, $C_{3-10}$ cycloalkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl and $C_{1-4}$ haloalkyl;

$R^{2q}$ is selected from $C_{1-6}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{3-6}$ cycloalkyl- $C_{1-6}$ alkyl, aryl, aryl($C_{1-4}$ alkyl), heteroaryl and heleroaryl ($C_{1-4}$ alkyl)-

and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group $C_{1-4}$ alkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy $C_{1-4}$ haloalkoxy, and dimethylamino;

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein $N_4$ in 1-piperiazinyl is substituted with 0-1 substituents selected from the group $R^{2t}$, $CO_2R^{2q}$, $COR^{2q}$ and $SO_2R^{2q}$;

$R^{2t}$ is selected from H, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy $-C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{3-6}$ cycloalkyl - $C_{1-6}$ alkyl, aryl, aryl ($C_{1-4}$ alkyl)-, heteroaryl and heteroaryl ($C_{1-4}$ alkyl);

$R^3$ is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, methylenedioxy, $C_{1-4}$ alkyloxy-$C_{1-4}$ alkyloxy, $-OR^{2m}$, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy, Br, Cl, F, I, -CN, dimethylamino, $CF_3$, $C_2F_5$, $OCF_3$, $SO_2Me$ and acetyl;

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl,

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benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substitued at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, F, I, $C_{1-4}$ haloalkyl, -CN, $NR^{2g}R^{2h}$, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, $COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{3a}$, $COR^{3a}$ and $SO_2R^{3a}$ wherein,

$R^{3a}$ is selected from the group $C_{1-6}$ alkyl, $C_{1-4}$ cycloalkyl-$C_{1-6}$ alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group $C_{1-4}$ alkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy, $C_{1-4}$ haloalkoxy, and dimethylamino;

$R^4$ and $R^5$ are independently selected at each occurrence from H, Br, Cl, F, I, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyloxy, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylsulfinyl, $C_{1-6}$ alkylsulfonyl, amino, $C_{1-4}$ alkylamino, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of $C_{1-7}$ alkyl, $C_{3-8}$ cycloalkyl, Br, Cl, F, I, -C(O)H, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy, $C_{1-4}$ haloalkoxy, $C_{1-4}$ alkylthio, $C_{1-4}$ alkylsulfinyl, $C_{1-4}$ alkylsulfonyl, $C_{1-6}$ alkylamino and $(C_{1-4}$ alkyl$)_2$ amino and wherein $R^4$ and $R^5$ non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, $-OC_{1-6}$-alkyl and $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{3-7}$ c-alkyl, $C_{1-6}$

alkyl$(OH)_nCO_2R$ wherein R is H or $C_{1-6}$ alkyl, $C_{1-6}$ alkyl$(OH)_n$ ,wherein n is 0-3 or $R^4$ and $R^5$ may join together to form a $C_{3-6}$ alkylene chain.

[13] The present invention also relates to a method as described directly above in group [12] wherein

$R^1$ is selected from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, $-XR^{1c}$ wherein $R^1$ is substituted with 0-6 substituents selected from halogen, $C_{1-4}$ alkyl or $C_{1-4}$ haloalkyl;

$R^2$ is selected from substituted-$C_{1-10}$ alkyl, branched $C_{3-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, $C_{3-8}$ cycloalkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl, $-NR^{2c}R^{2d}$ wherein, in the case of substituted-$C_{1-10}$ alkyl, 1-3 substitutents are independently selected from the group $R^{2i}$, $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{21}$ and in wich 0-1 carbons of $C_{4-8}$ cycloalkyl is replaced by -O- and wherein the $R^2$ groups, other than substituted-$C_{1-10}$ alkyl, are substituted with 0-3 substituents independently selected from the group $R^{2i}$, $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{21}$ and in wich 0-1 carbons of $C_{4-8}$ cycloalkyl is replaced by -O-.

[14] The present invention also relates to a method described directly above in [12] or [13] wherein $R^3$ is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

[15] The present invention relates to a method described directly above in groups [12]-[14] wherein $R^3$ is substituted with 0-4 substituents independently selected from halogen, $C_{1-4}$ alkyloxy, $C_{1-6}$ alkyl or NR'R" wherein R' and R" are independently selected from H or $C_{1-6}$ alkyl.

[16] The present invention preferrably relates to a method as described directly above in groups [12]-[15] wherein $R^3$ is selected from 2,4-dichlorophenyl, 2-chloro-4-methoxyphenyl, 2,4,6-trimethylphenyl, 2,4,6-trimethoxyphenyl, 2-dimethylamino-4-methyl-pyridin-5-yl, 2,4-dichloro-5-fluorophenyl, 2-chloro-4-methoxy-5-fluorophenyl, 2-chloro-4,5-dimethoxyphenyl or 2-chloro-4,5-dimethoxyphenyl.

[17] The present invention also preferrably relates to a method as described in groups [13]-[15] wherein $R^2$ is selected from $C_1$ alkyl of the formula -CR'R"R"' wherein R', R" and R"' are independently selected from H, $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, hydroxy$C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{1-6}$ alkyloxy, hydroxy, with the proviso that each of R',R" and R'" cannot be H;

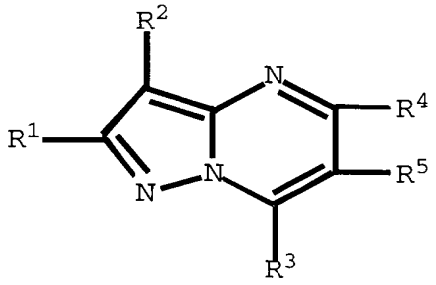
or $R^2$ is selected from NR'R" wherein R' and R" are independently selected from H or $C_{1-6}$ alkyl.

[18] The present invention preferrably relates to a method according to groups [13]-[17] wherein $R^3$ is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom wherein, aryl is phenyl, each phenyl being substituted with 0-5 substituents independently selected at each occurrence from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, methylenedioxy, $C_{1-4}$

alkyloxy-$C_{1-4}$ alkyloxy, $-OR^{2m}$, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy, Br, Cl, F, I, -CN, dimethylamino, $CF_3$, $C_2F_5$, $OCF_3$, $SO_2Me$ and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substitued at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, $COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each pyridyl being substituted at any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{3a}$, $COR^{3a}$ and $SO_2R^{3a}$ .

[19] The present invention preferrably relates to a method of antagonizing a CRF-1 receptor in mammals including humans wherein binding to the receptor causes and ultimately results in the treatment of affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders

induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein

$R^1$ is selected from $C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy, -SH or OH;

$R^2$ is selected from $C_{1-4}$ alkyl which is unsubstituted or substituted with 1-4 substitutents selected from $C_{1-6}$ alkyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyl$OR^{2g}$, $C_{2-6}$ alkenyl or $OR^{2g}$ wherein $R^{2g}$ is H or $C_{1-6}$ alkyl;

$R^3$ is selected from an aryl or heteroaryl group bonded through an unsaturated carbon atom that is unsubstituted or substituted with 1-4 substituents selected from Cl, F, I, Br, -OH, $CF_3$, $S(O)_nC_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $C_{1-6}$ alkyl or $NR^{2g}R^{2h}$ wherein $R^{2g}$ and $R^{2h}$ are independently selected from H or $C_{1-6}$ alkyl;

$R^4$ and $R^5$ are independently selected from H, $C_{1-6}$ alkyl or $C_{1-6}$ alkyloxy.

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[20] The present invention also relates to a method according to group [19] wherein $R^3$ is substituted with 2-4 substituents.

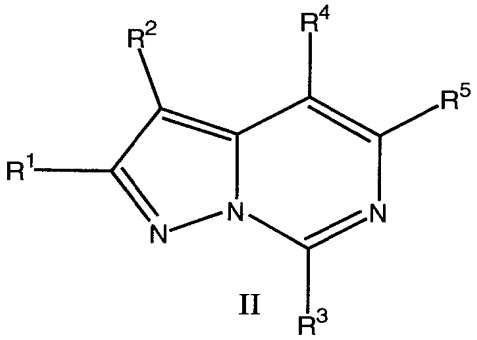
[21] The present invention also relates to a method according to group [19]-[20] wherein $R^2$ is substituted with 1-4 substituents.

[22] The present invention also relates to a method according to group [19]-[21] using the formulae shown in Table 1.

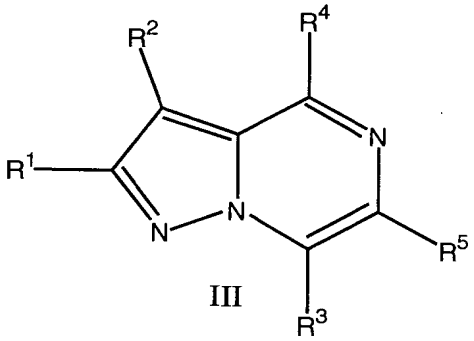
[23] The present invention also provides pharmaceutical compositions comprising compounds of Formula (1) with the variables as recited above in group [1] and [1'] with the proviso that the compounds excluded in proviso (d) in group [1] are included herein and a pharmaceutically acceptable carrier.

[24] The preferred pharmaceutical compositions include those compounds as shown in groups [1'] and [2]-[11] along with a pharmaceutically acceptable carrier.

[25] The present invention also relates to a compound of the formulae shown below having the variables recited above in groups [1'] and [1]-[24]:




II




III

except that the provisos listed in group I are not included for the compounds of formula II and III.

[26] The present invention further comprises a compound of formula II or III in combination with a pharmaceutically acceptable excipient to form a pharmaceutical composition.

[27] The present invention further relates to a method of treating CRF related disorders or conditions or use in therapy of compounds of formula II or III comprising administering a compound of formula II or III with the variables for $R^1$-$R^5$ as shown above in groups [1'] and [1]-[24] to a patient in need of treatment thereof.

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

The term "alkyl", unless otherwise specified, includes both branched and straight-chain alkyl having the specified number of carbon atoms. "Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any

stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of formulas (I). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl

acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety, depression, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a host.

The term "registry reference" refers to computer search generated sources of known chemical structures as identified by specific structure herein.

Compounds prepared according to the synthetic schemes and examples include, without limitation, those compounds specifically set forth in Table 1, hereinbelow, as well as the following:

7-(2,4-dichloro-5-fluorophenyl)-2-ethyl-3-(2-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-6-methyl-3-(2-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2-chloro-4-methoxyphenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine-3-carboxaldehyde

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxyethyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-ethyl-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-ethylpyrazolo[1,5-a]pyrimidine

2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(3-pentyl)-pyrazolo[1,5-a]pyrimidine

2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(2-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dimethylphenyl)-2-ethyl-3-(2-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-5-methylthio-3-(2-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(6-methyl-5-hepten-2-yl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-4-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(3-

pentyl)pyrazolo[1,5-a]pyrimidine

7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine

7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine

7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine

7-(2,4-dimethylphenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine

4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidinyl)pentanoic acid

4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidinyl)-N-methylpentanamide

3-(5-(benzoxazol-2-ylthio)-2-pentyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine

3-(5-(benzoxazolidinethione-3-yl)-2-pentyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-2-propyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-3-(1-ethoxy-2-propyl)-2-ethyl-pyrazolo[1,5-a]pyrimidine

3-(1-acetoxy-2-propyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine

3-(1-acetoxy-2-butyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-3-butyl)pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-methoxy-3-butyl)pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-6-methyl-pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(3-heptyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-6-methyl-pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine

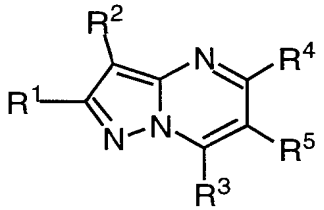
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine

## Synthesis

Compounds of formula (I) can be prepared by the following synthetic routes and schemes. Where a detailed description is not provided, it is assumed that those skilled in the art of organic synthesis will readily understand the meaning.

Synthesis of compounds of formula (I) may be prepared by the reaction shown in Scheme 1.

The embodiment of this invention concerning compounds of Formula (I) with the structure




may be prepared according to the following methods:

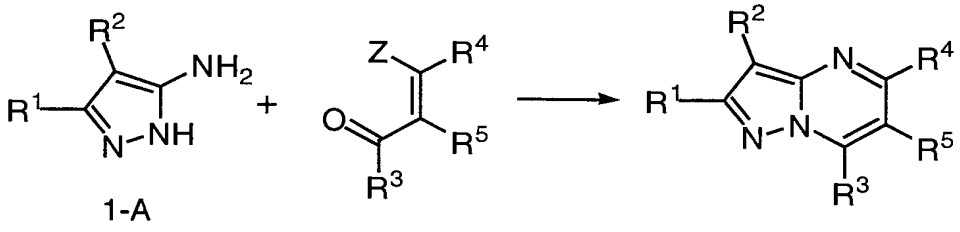
The pyrazolo[1,5-a]pyrimidine ring system is best prepared by the condensation reaction of a 3-aminopyrazole (1-A, Scheme 1A) with a compound of formula

57

1-B. Here, Z is ethoxy or dimethylamino, and compound 1-B may be prepared by the reaction of a compound of formula $R^3C(=O)CH_2R^6$ with a reagent of formula $R^5C(Z)(OEt)_2$. These types of reactions are normally done by heating the two compounds (as a 1:1 mixture) without solvent, and distilling off the volatile components after the reaction is complete. The reaction between 1-A and 1-B is conveniently performed in a solvent such as acetic acid with heating; the acetic acid acts as both solvent and catalyst for the condensation.

Preparation of the pyrazoles can begin with the acylation of a nitrile compound 1-C (Scheme 1B). Normally, a strong base, such as lithium diisopropylamide, is used to deprotonate the nitrile, and the resulting anionic intermediate is treated with a carboxylic ester $R^1CO_2Et$ or

Scheme 1A

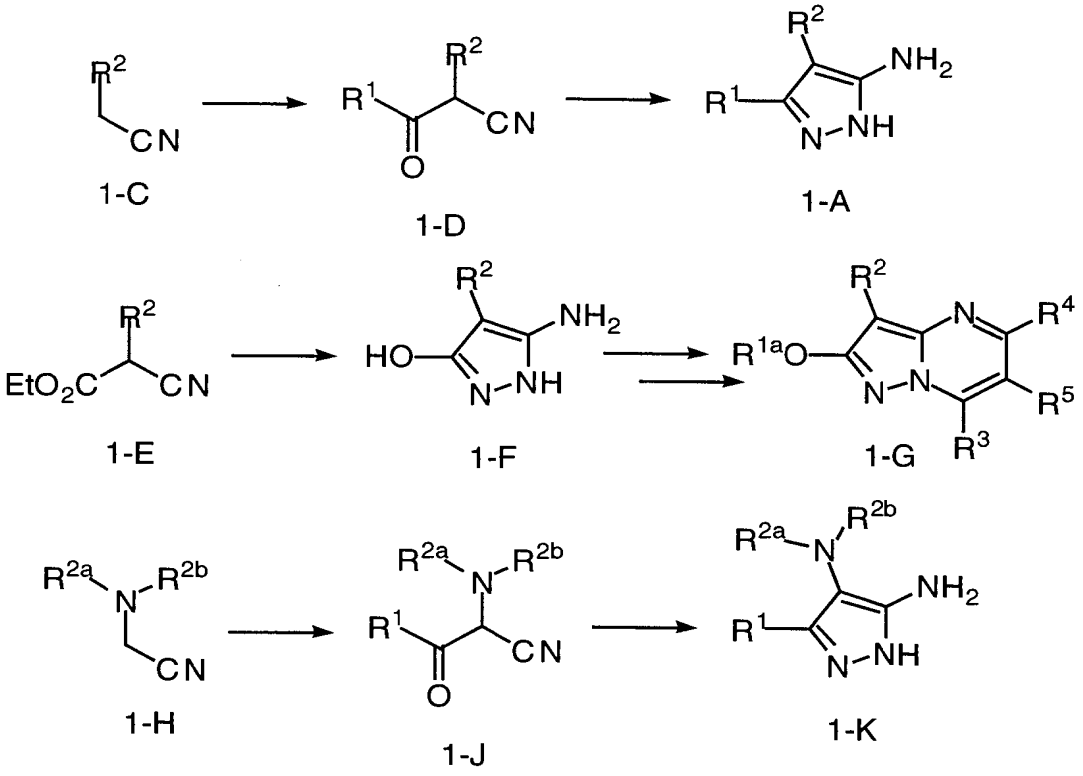



1-A 1-B

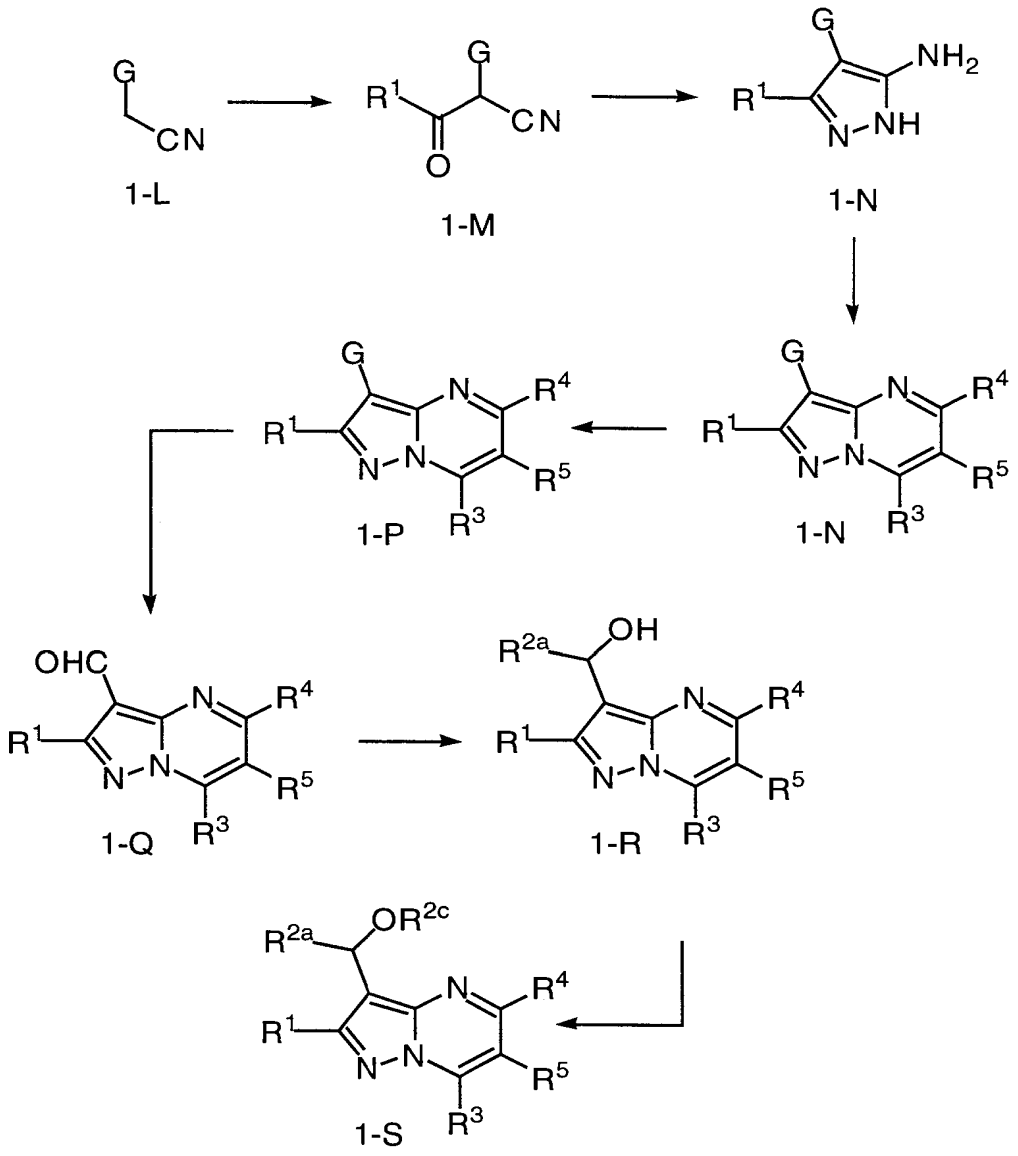
acid chloride $R^1COCl$ to generate the ketonitrile 1-D. Condensation of this compound with hydrazine then gives the aminopyrazole. This reaction may be performed in refluxing alcoholic solvent with the optional presence of an acid catalyst, such as acetic acid. Heteroatomic versions of this route are possible. Aminopyrazoles with an $R^1$ group wherein $R^1 = R^{1a}O$ may be prepared by starting with cyanoacetic esters like 1-E, which react with hydrazine to afford 3-amino-5-hydroxypyrazole 1-F.

Cyclization with reagent 1-B and O-alkylation with a reagent $R^{1a}X$, wherein X is a halide or pseudohalide group, gives compound 1-G. Finally, strong base treatment of aminonitrile 1-H, usually in the presence of a solvent mixture such as THF/HMPA, followed by acylation and ring-forming, gives diamine 1-K.

Scheme 1B



Scheme 1C



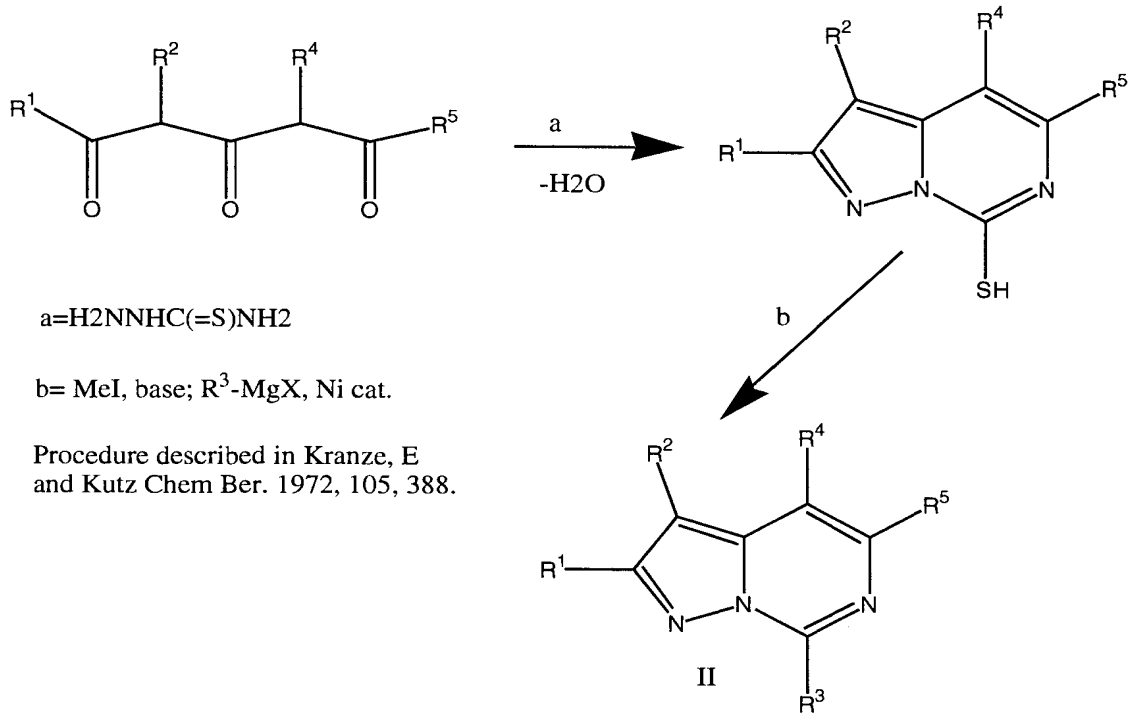

Scheme 1C shows one application of a variation involving a group G (carboalkoxy or CN) which can serve as a functional handle for various $R^2$ substitutions. Since G is activating, the acylation of 1-L to give 1-M may not require as strong a base as is used for the transformation of 1-C to 1-D; a reagent such as an orthoester may also be used. Subsequent ring condensations to 1-N and then to 1-P proceed as described earlier. Then, the group G is converted to the $R^2$ group of

choice wherein $R^2$ and substituted versions thereof is as defined in the claims and as above in the specification; the following method is one example. Use of a reducing agent such as diisobutylaluminum hydride in a solvent like toluene or dichloromethane at low temperatures can be used to obtain the aldehyde 1-Q. The aldehyde may be allowed to react with organometallic reagents such as the Grignard reagent $R^{2a}MgBr$ to afford the alcohol 1-R. The hydroxy group may then be O-alkylated (typically using a reagent $R^{2c}X$ and a base such as sodium hydride in a polar aprotic solvent such as DMF) to give the compound 1-S. Other such manipulations of the G group should be familiar to those skilled in the art of organic synthesis.

Similarly, the remaining variables in the starting materials described above such as $R^1$ or $R^3$ are determined based upon the desired target moiety. Thus, varying the ketone 1-B with respect to the aryl or heteroaryl group $R^3$ permits synthesis of a compound of formula I having $R^3$ as the desired heteroaryl or aryl group and substituted versions thereof as recited in the claims and above text and as further shown in the examples and table before the appended claims.

The synthesis of compounds of formula II or III may be accomplished by the general schemes shown below in Scheme 2 and in Scheme 3.

SCHEME 2




a=H2NNHC(=S)NH2

b= MeI, base; $R^3$-MgX, Ni cat.

Procedure described in Kranze, E and Kutz Chem Ber. 1972, 105, 388.

II

The variables for $R^1$-$R^5$ are selected from those variables as defined in any of the groups [1]-[24]. The compound of formula II is prepared by starting with the acyclic triketo intermediate shown above which is reacted with reagent a to form the bicyclic intermediate which is then treated with the grignard reagent b to form a compound of formula II.

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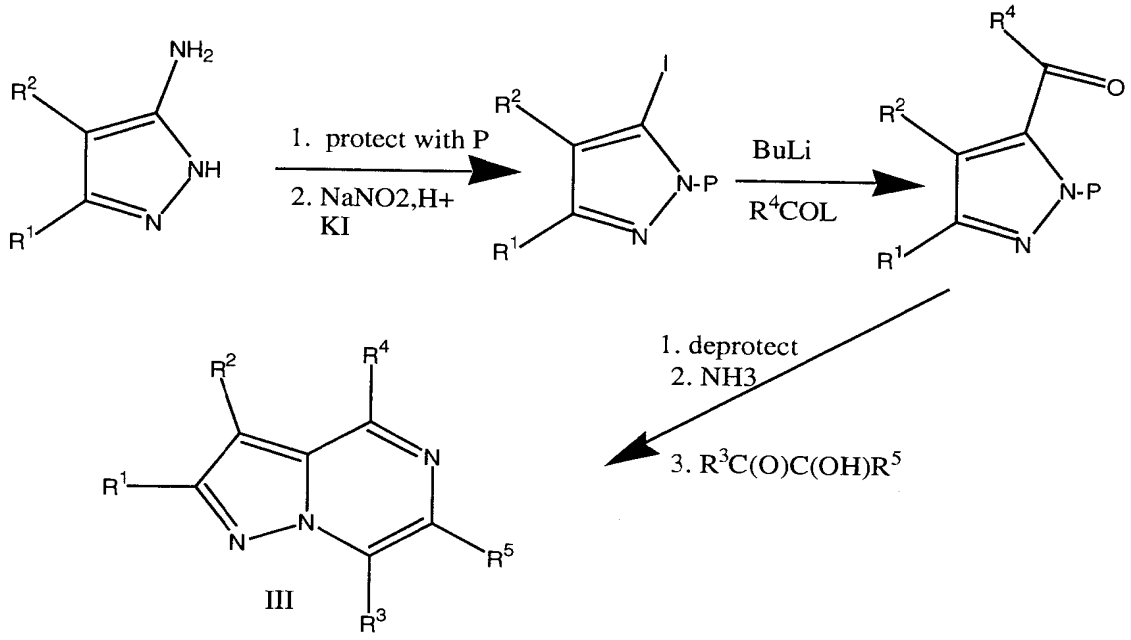
SCHEME 3




The variables for $R^1$-$R^5$ in Scheme 3 are selected from those described in groups [1]-[24]. Compounds II and III with the variables as defined above are useful as CRF antagonists.

## Utility

### CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

Radioligand binding experiments

Compounds of the invention were tested for in vitro activity as CRF receptor antagonists. The tests described below demonstrated that the examples tested had $K_i$s of 10,000 nM or less and are thus useful as CRF receptor antagonists. Preferred antagonists have or will have a $K_i$ of 1,000 nM or less. Radioligand binding experiments were performed with membranes from rat

frontal cortex to determine binding affinities ($K_i$'s) of test compounds for the rat $CRH_1$ receptor using a modified version of methods described earlier (see E.B. DeSouza, J. Neurosci, 7:88, 1987). Rat cortex was homogenized in tissue buffer (containing 50 mM HEPES, 10 mM $MgCl_2$, 2 mM EGTA, and 1 µg/ml each of aprotonin, leupeptin, and pepstatin, pH 7.0 @ 23°C) using a Brinkman Polytron (PT-10, setting 6 for 10 sec). The homogenate was centrifuged at 48,000 X g for 12 min and the resulting pellet was washed by two sequential re-suspension and centrifugation steps. The final pellet was suspended to tissue buffer to a working concentration of 0.1 mg/ml protein. Protein determinations were made using the bicinchoninic acid (BCA) assay (Pierce, Rockford, IL) with bovine serum albumin as the standard.

All test compounds were prepared in assay buffer, which was identical to the tissue buffer except for the inclusion of 0.15 mM bacitracin and 0.1% w/v ovalbumin. Binding assay were conducted in disposable polypropylene 96-well plates (Costar Corp., Cambridge, MA) and initiated by the addition of 100 µl membrane homogenate (containing 40-60 µg protein) to 200 µl of assay buffer containing radioligands (150 pM, final concentration, [$^{125}$I] tyr° ovine CRH; New England Nuclear, MA) and competing test compounds. Specific binding was determined in the presence of 10 µM α-helical CRH. Competition experiments were conducted using 12 concentrations of ligand (ranging from 1 X $10^{-11}$ to 1 X $10^{-5}$ M). The reactions mixtures were incubated to equilibrium for 2 hr at 23°C and terminated by rapid filtration using a cell harvester (Inotech Biosystems Inc., Lansing MI) over GFF glass-fibers (pre-soaked in 0.3 % v/v polyethyleneimine). Filters were rapidly washed 3X with 0.3 ml cold wash buffer (PBS, pH 7.0, containing 0.01% Triton X-100), dried, and counted in a gamma counter at 80% efficiency.

Binding affinities ($K_i$'s) of ligands for the $CRH_1$ receptor were calculated using the iterative nonlinear regression curve-fitting programs (LIGAND) of Munson and Rodbard (Anal. Biochem. 1980, 107, 220-239) or Prism (GraphPad Prism, San Diego, CA). Data were best-fit by the one-site/state competition equation.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. Synapse 1:572 (1987). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range $10^{-9}$ to $10^{-6m}$) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/$^{32}$P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 µl of [$^3$H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [$^{32}$P]cAMP from [$^{32}$P]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

The in vivo activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention

have been outlined in C.W. Berridge and A.J. Dunn Brain Research Reviews 15:71 (1990).

Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the treatment of inbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be

present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as

benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The preferred indication and use of the compounds and compositions of the invention is in the treatment of depression or anxiety.

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

Examples

The following specific synthetic example describes the procedures which, when applied to appropriately substituted substrates, may be employed in the synthesis of the compounds in Table 1.

Example 1

Preparation of 7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine

Part A. A mixture of 2-ethyl-1-bromobutane (10.0 mL, 71.4 mmol), potassium cyanide (14.0 g, 215 mmol) and aliquat 336 (10 drops) in 50 mL water was heated to reflux overnight with vigorous stirring. The mixture was cooled, and extracted with dichloromethane (2 x 50 mL). The extracts were combined, dried over magnesium sulfate, filtered and evaporated. The residual liquid was distilled bulb-to-bulb to afford pure product, 3-ethylpentanenitrile (5.50 g, 49.5 mmol, 69%). b.p. 40-45 °C (5 mm Hg). Spectral data: $^1$H NMR (300 MHz, $CDCl_3$): δ 2.33 (2H, d, J = 5.8 Hz), 1.62-1.36 (5H, m), 0.92 (6H, t, J = 7.3 Hz). MS ($H_2O$-GC/MS): m/e 112 (100).

Part B. A solution of diisopropylamine (7.50 mL, 57.2 mmol) in THF (100 mL) was cooled to -78 °C, and treated

with n-butyllithium (34.0 mL of a 1.6 M solution in hexane). The solution was warmed briefly to 0 °C, and then recooled to -78 °C. The nitrile compound from Part A was then added by syringe, and the solution was allowed to stir for 1 hour. Then, ethyl propionate (6.50 mL, 56.7 mmol) was added by syringe, and the resulting mixture was allowed to stir and warm to ambient temperature for 12 hours. It was poured into 200 mL of satd. aq. $NH_4Cl$ solution, and this was extracted with ethyl acetate (2 x 200 mL). The extracts were combined, dried over magnesium sulfate, filtered and evaporated. The residual oil was separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to afford the product, 4-cyano-5-ethyl-3-heptanone, as an oil 4.06 g, 24.3 mmol, 49%). TLC $R_F$ 0.47 (20:80 ethyl acetate-hexane). Spectral data: $^1H$ NMR (300 MHz, $CDCl_3$): δ 3.49 (1H, d, J = 4.4 Hz), 2.74 (2H, q, J = 7.3 Hz), 2.08-1.98 (1H, m), 1.70-1.58 (1H, m), 1.50-1.20 (3H, m), 1.12 (3H, t, J = 7.3 Hz), 0.95 (3H, t, J = 7.3 Hz), 0.91 (3H, t, J = 7.3 Hz). MS ($H_2O$-GC/MS): m/e 167 (100).

Part C. A solution of the ketonitrile from Part B (4.06 g, 24.3 mmol), hydrazine hydrate (2.70 mL, 55.7 mmol) and acetic acid (5.00 mL, 83.7 mmol) in benzene (50 mL) was heated to reflux under a Dean-Stark trap with azeotropic distillation of water. After being heated for 12 hours, the mixture was cooled and poured into 100 mL 1 N aq. $NaHCO_3$ solution. This was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed in sequence with brine, combined, dried over sodium sulfate, filtered and evaporated to afford sufficiently-pure product, 3-amino-5-ethyl-4-(3-pentyl)pyrazole, as a viscous oil (2.48 g,

13.7 mmol, 56%). Spectral data: $^1$H NMR (300 MHz, $CDCl_3$): δ 3.48 (2H, br), 2.54 (2H, q, J = 7.3 Hz), 2.25-2.14 (1H, m), 1.71-1.49 (4H, m), 1.20 (3H, t, J = 7.3 Hz), 0.83 (6H, t, J = 7.3 Hz), 1H missing. MS ($NH_3$-CI): m/e 183 (12), 182 (100).

Part D. A mixture of 2,4-dichloroacetophenone (10.0 g, 52.9 mmol) and dimethylformamide diethyl acetal (10.0 mL, 58.3 mmol) was heated to reflux for 12 hours, then cooled and evaporated under high vacuum. The residual oil was separated by column chromatography (silica gel, 1:1 ethyl acetate-hexane) to afford the product, 1-(2,4-dichlorobenzoyl)-2-(N,N-dimethylamino)ethene, as a viscous oil (12.11 g, 49.6 mmol, 94%). TLC $R_F$ 0.05 (20:80 ethyl acetate-hexane). Spectral data: $^1$H NMR (300 MHz, $CDCl_3$): δ 7.40 (1H, d, J = 2.2 Hz), 7.38-7.23 (3H, m), 5.33 (1H, d, J = 12.4 Hz), 3.11 (3H, br s), 2.89 (3H, br s). MS ($NH_3$-CI): m/e 249 (1), 248 (10), 247 (8), 246 (64), 245 (16), 244 (100).

Part E. A solution of the product of Part C (2.25 g, 1.38 mmol) and that of Part D (0.337 g, 1.38 mmol) in acetic acid (5 mL) was heated to reflux for 10 hours, then cooled, and poured into water. This was neutralized by the addition of solid sodium bicarbonate until the evolution of $CO_2$ subsided. The resulting mixture was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed with brine (100 mL), combined, dried over sodium sulfate, filtered and evaporated. The resulting mixture of regioisomeric products (ca. 5:1 estimated by TLC visualization) were separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to afford the major regioisomer as the more TLC-mobile

product, which was the title compound. TLC $R_f$ 0.32 (10:90 ethyl acetate-hexane). Spectral data: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.38 (1H, d, J = 4.1 Hz), 7.58 (1H, d, J = 2.0 Hz), 7.55 (1H, d, J = 8.2 Hz), 7.41 (1H, dd, J = 8.2, 2.0 Hz), 6.65 (1H, d, J = 4.1 Hz), 2.79 (2H, q, J = 7.7 Hz), 2.78-2.68 (1H, m), 2.03-1.79 (4H, m), 1.25 (3H, t, J = 7.7 Hz), 0.83 (6H, t, J = 7.3 Hz). MS ($NH_3$-CI): m/e 367 (2), 366 (11), 365 (15), 364 (65), 363 (25), 362 (100). Analysis calc'd for $C_{19}H_{21}Cl_2N_3$: C, 62.99; H, 5.84; N, 11.60; found: C, 62.97; H, 5.74; N, 11.49.

Examples 2-30 were prepared and/or may be prepared in an analogous fashion.

Example 31

Preparation of 7-(2,4-dichlorophenyl)-3-(N,N-diethylamino)-2-ethylpyrazolo[1,5-a]pyrimidine

Part A. A solution of diisopropylamine (10.0 mL, 76.3 mmol) in THF (60 mL) was cooled to -78 °C, and treated with n-butyllithium (50.0 mL of a 1.6 M solution in hexane). The solution was warmed briefly to 0 °C, and then recooled to -78 °C. To this was added first, N,N'-dimethylpropyleneurea as cosolvent (15 mL), then, diethylaminoacetontrile (10.0 mL, 74.1 mmol), and the solution was allowed to stir for 1 hour. Then, ethyl propionate (10.0 mL, 87.2 mmol) was added by syringe, and the resulting mixture was allowed to stir and warm to ambient temperature for 12 hours. It was poured into 200 mL of satd. aq. $NH_4Cl$ solution, and this was extracted with ethyl acetate (2 x 200 mL). The extracts were combined, dried over magnesium sulfate, filtered and evaporated. The residual oil was separated by column chromatography (silica gel, 20:80 ethyl acetate-hexane) to afford the product, 2-(N,N-diethylamino)-3-oxopentanenitrile, as an oil (5.31 g, 31.6 mmol, 43%).

Part B. A solution of the ketonitrile from Part A, hydrazine hydrate (3.00 mL, 61.9 mol) and acetic acid (6.00 mL, 104 mmol) in benzene (100 mL) was heated to reflux under a Dean-Stark trap with azeotropic removal of water for a period of 14 hours. Excess hydrazine (2 mL) and excess acetic acid (5 mL) were then added, and refluxing was allowed to continue for 20 hours. The solution was cooled and poured into 200 mL 1 N aq. $NaHCO_3$ solution. This was extracted with ethyl acetate (2 x 200

mL), and the extracts were washed in sequence with brine, combined, dried over sodium sulfate, filtered and evaporated. The residue was separated by column chromatography (silica gel, 30:70 ethyl acetate to remove unreacted starting material, then ethyl acetate) to afford the product, 3-amino-4-(N,N-diethylamino)-5-ethylpyrazole, as a viscous oil which darkens in air (750 mg, 4.41 mmol, 15%).

Part C. A solution of the diamine from Part B (300 mg, 1.76 mmol) and 1-(2,4-dichlorobenzoyl)-2-(N,N-dimethylamino)ethene (470 mg, 1.93 mmol) in acetic acid (5 mL) was heated to 100 °C for 10 hours, then cooled and poured into satd. aq. NaHCO3 solution (100 mL). This mixture was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed with brine, combined, dried over sodium sulfate, filtered and evaporated. The residual oil was separated by columnm chromatography (silica gel, 20:80 ethyl acetate-hexane) to afford the title product as a red oil (411 mg, 1.13 mmol, 64%). Spectral data: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.38 (1H, d, J = 4.0 Hz), 7.58 (1H, d, J = 1.8 Hz), 7.56 (1H, d, J = 8.4 Hz), 7.42 (1H, dd, J = 8.4, 1.8 Hz), 6.65 (1H, d, J = 4.0 Hz), 3.27 (4H, q, J = 7.3 Hz), 2.80 (2H, q, J = 7.3 Hz), 1.26 (3H, t, J = 7.3 Hz), 1.00 (6H, t, J = 7.3 Hz). MS ($NH_3$-CI): calculated for $C_{18}H_{21}Cl_2N_4$ 363.1143, measured 363.1146; m/e 367 (6), 366 (14), 365 (81), 364 (28), 363 (100).

Examples 32-45 were and/or may be prepared in an analogous manner.

Examples 51 and 92

Preparation of 7-(2,4-dichlorophenyl)-2-hydroxy-6-methyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine (92) and 7-(2,4-dichlorophenyl)-2-methoxy-6-methyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine (51)

Part A. A solution of triphenylphosphine (25.0 g, 95.3 mmol) in THF (200 mL) was cooled to -30 °C, and diethyl azodicarboxylate (15.0 mL, 95.2 mmol) was slowly added dropwise in conc. THF solution. After the addition was complete, the mixture was treated with a THF solution of 3-pentanol (10.0 mL, 90.6 mmol) and ethyl cyanoacetate (10.0 mL, 92.1 mmol). The resulting mixture was allowed to stir and warm to ambient temperature for 12 hours, then was evaporated. The residual oil was separated by column chromatography (10:90 ethyl acetate-hexane) to afford the product, ethyl 2-cyano-3-ethylpentanoate, as a viscous oil (3.41 g, 18.6 mmol, 21%). TLC $R_F$ 0.43 (20:80 ethyl acetate-hexane). Spectral data: $^1$H NMR (300 MHz, $CDCl_3$): δ 4.27 (2H, q, J = 7.0 Hz), 3.61 (1H, d, J = 4.4 Hz), 2.04-1.93 (1H, m), 1.70-1.35 (4H, m), 1.33 (3H, t, J = 7.0 Hz), 0.97 (3H, t, J = 7.3 Hz), 0.94 (3H, t, J = 7.3 Hz). MS ($H_2O$-GC/MS): m/e 185 (8), 184 (100).

Part B. A solution of the cyanoester from Part A and hydrazine hydrate (2.00 mL, 41.2 mmol) in ethanol (30 mL) was heated to reflux for 10 hours. The solution was cooled, and poured into water. This was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed with brine, combined, dried over sodium sulfate, filtered and evaporated. The resulting oil was sufficiently pure product, 3-amino-5-hydroxy-4-(3-pentyl)pyrazole (1.29 g, 7.62 mmol, 41%).

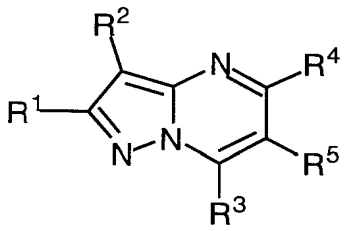
Part C. A solution of the pyrazole compound from Part B (478 mg, 2.82 mmol) and 2-(2,4-dichlorobenzoyl)-1-(N,N-dimethylamino)-1-propene (729 mg, 2.82 mmol) in acetic acid (10 mL) was heated to reflux for 10 hours. The solution was cooled and poured into water (100 mL). This was neutralized by the addition of solid $NaHCO_3$, and the mixture was extracted with ethyl acetate (2 x 100 mL). The extracts were washed with brine, combined, dried over sodium sulfate, filtered and evaporated. The residue was separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to give the compound of Example 92 as a solid (210 mg, 0.576 mmol, 20%). m.p. 227-228 °C. TLC $R_F$ 0.46 (20:80 ethyl acetate-hexane). Spectral data: $^1$H NMR (300 MHz, $CDCl_3$): δ 10.53 (1H, br s), 8.27 (1H, s), 7.63 (1H, d, J = 2.2 Hz), 7.45 (1H, dd, J = 8.4, 2.2 Hz), 7.25 (1H, d, J = 8.4 Hz), 2.72-2.62 (1H, m), 2.02 (3H, s), 1.77-1.65 (4H, m), 0.82 (6H, t, J = 7.5 Hz). MS (ESI): m/e 366 (69), 364 (100).

Part D. A solution of the compound of Example 92 (31 mg, 0.085 mmol) and Proton-Sponge™ (20 mg, 0.093 mmol) in acetonitrile (2 mL) was cooled to 0 °C, and treated with methyl methanetrifluorosulfonate (10 µL, 0.088 mmol). After stirring for 10 hours and warming to ambient temperature, the mixture was evaporated, and the residue was separated directly by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to give the compound of Example 51 as a viscous oil (7 mg, 0.019 mmol, 22%). TLC $R_F$ 0.55 (20:80 ethyl acetate-hexane). Spectral data: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.27 (1H, s), 7.60 (1H, d, J = 2.2 Hz), 7.43 (1H, dd, J = 8.0, 2.0 Hz), 7.32 (1H, d, J = 8.0 Hz), 3.84 (3H, s), 2.80-2.70 (1H, m), 2.08 (3H, s), 1.86-1.70 (4H, m), 0.82 (6H, t, J = 7.4 Hz). MS ($NH_3$-CI): m/e

383 (2), 382 (12), 381 (14), 380 (65), 379 (25), 378 (100).

Examples 52-90 and 92 were and/or may be prepared according to the procedures described above. The additional examples prepared or readily prepared (93-281) were (or may be) prepared according to the procedures described above and shown in the general schemes and described in the text. Table 1 shows the preferred compounds.

Table 1



| Ex No | $R^1$ | $R^2$ | $R^4$ | $R^5$ | $R^3$ | m.p. °C |
|---|---|---|---|---|---|---|
| 1 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2,4-$Cl_2$-$C_6H_3$ | oil[a] |
| 2 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | 88-89 |
| 3 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | oil[b] |
| 4 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | 166-167 |
| 5 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 6 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | $CH_3$ | 2,4-$Cl_2$-$C_6H_3$ | 90-91 |
| 7 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | $CH_3$ | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 8 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | $CH_3$ | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 9 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | $CH_3$ | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 10 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | $CH_3$ | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 11 | $C_2H_5$ | $(C_2H_5)_2CH$ | $CH_3$ | H | 2,4-$Cl_2$-$C_6H_3$ | - |
| 12 | $C_2H_5$ | $(C_2H_5)_2CH$ | $CH_3$ | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 13 | $C_2H_5$ | $(C_2H_5)_2CH$ | $CH_3$ | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 14 | $C_2H_5$ | $(C_2H_5)_2CH$ | $CH_3$ | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 15 | $C_2H_5$ | $(C_2H_5)_2CH$ | $CH_3$ | H | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 16 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2,4-$Cl_2$-$C_6H_3$ | oil[c] |
| 17 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 18 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | oil[d] |
| 19 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| 20 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 21 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | $CH_3$ | 2,4-$Cl_2$-$C_6H_3$ | 78-79 |
| 22 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | $CH_3$ | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 23 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | $CH_3$ | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 24 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | $CH_3$ | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 25 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | $CH_3$ | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 26 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | $CH_3$ | H | 2,4-$Cl_2$-$C_6H_3$ | - |
| 27 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | $CH_3$ | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 28 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | $CH_3$ | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 29 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | $CH_3$ | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 30 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | $CH_3$ | H | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 31 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2,4-$Cl_2$-$C_6H_3$ | oil[e] |
| 32 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | 97-98 |
| 33 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 34 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 35 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 36 | $C_2H_5$ | $(C_2H_5)_2N$ | H | $CH_3$ | 2,4-$Cl_2$-$C_6H_3$ | - |
| 37 | $C_2H_5$ | $(C_2H_5)_2N$ | H | $CH_3$ | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 38 | $C_2H_5$ | $(C_2H_5)_2N$ | H | $CH_3$ | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 39 | $C_2H_5$ | $(C_2H_5)_2N$ | H | $CH_3$ | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 40 | $C_2H_5$ | $(C_2H_5)_2N$ | H | $CH_3$ | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 41 | $C_2H_5$ | $(C_2H_5)_2N$ | $CH_3$ | H | 2,4-$Cl_2$-$C_6H_3$ | - |
| 42 | $C_2H_5$ | $(C_2H_5)_2N$ | $CH_3$ | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 43 | $C_2H_5$ | $(C_2H_5)_2N$ | $CH_3$ | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 44 | $C_2H_5$ | $(C_2H_5)_2N$ | $CH_3$ | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| 45 | $C_2H_5$ | $(C_2H_5)_2N$ | $CH_3$ | H | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 46 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2,4-$Cl_2$-$C_6H_3$ | - |
| 47 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 48 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 49 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 50 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 51 | $OCH_3$ | $(C_2H_5)_2CH$ | H | $CH_3$ | 2,4-$Cl_2$-$C_6H_3$ | oil[f] |
| 52 | $OCH_3$ | $(C_2H_5)_2CH$ | H | $CH_3$ | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 53 | $OCH_3$ | $(C_2H_5)_2CH$ | H | $CH_3$ | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 54 | $OCH_3$ | $(C_2H_5)_2CH$ | H | $CH_3$ | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 55 | $OCH_3$ | $(C_2H_5)_2CH$ | H | $CH_3$ | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 56 | $OCH_3$ | $(C_2H_5)_2CH$ | $CH_3$ | H | 2,4-$Cl_2$-$C_6H_3$ | - |
| 57 | $OCH_3$ | $(C_2H_5)_2CH$ | $CH_3$ | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 58 | $OCH_3$ | $(C_2H_5)_2CH$ | $CH_3$ | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 59 | $OCH_3$ | $(C_2H_5)_2CH$ | $CH_3$ | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 60 | $OCH_3$ | $(C_2H_5)_2CH$ | $CH_3$ | H | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 61 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | H | 2,4-$Cl_2$-$C_6H_3$ | - |
| 62 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 63 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 64 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 65 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-$(CH_3)_2$N-4-$CH_3$-pyridin-5-yl | - |
| 66 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | $CH_3$ | 2,4-$Cl_2$-$C_6H_3$ | - |
| 67 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | $CH_3$ | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 68 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | $CH_3$ | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 69 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | $CH_3$ | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 70 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | $CH_3$ | 2-$(CH_3)_2$N-4-$CH_3$- | - |

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|---|---|---|---|---|---|---|
| | | | | | pyridin-5-yl | |
| 71 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | $CH_3$ | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 72 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | $CH_3$ | H | $2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$ | - |
| 73 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | $CH_3$ | H | $2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$ | - |
| 74 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | $CH_3$ | H | $2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$ | - |
| 75 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | $CH_3$ | H | $2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl | - |
| 76 | $OCH_3$ | $(C_2H_5)_2N$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 77 | $OCH_3$ | $(C_2H_5)_2N$ | H | H | $2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$ | - |
| 78 | $OCH_3$ | $(C_2H_5)_2N$ | H | H | $2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$ | - |
| 79 | $OCH_3$ | $(C_2H_5)_2N$ | H | H | $2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$ | - |
| 80 | $OCH_3$ | $(C_2H_5)_2N$ | H | H | $2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl | - |
| 81 | $OCH_3$ | $(C_2H_5)_2N$ | H | $CH_3$ | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 82 | $OCH_3$ | $(C_2H_5)_2N$ | H | $CH_3$ | $2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$ | - |
| 83 | $OCH_3$ | $(C_2H_5)_2N$ | H | $CH_3$ | $2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$ | - |
| 84 | $OCH_3$ | $(C_2H_5)_2N$ | H | $CH_3$ | $2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$ | - |
| 85 | $OCH_3$ | $(C_2H_5)_2N$ | H | $CH_3$ | $2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl | - |
| 86 | $OCH_3$ | $(C_2H_5)_2N$ | $CH_3$ | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 87 | $OCH_3$ | $(C_2H_5)_2N$ | $CH_3$ | H | $2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$ | - |
| 88 | $OCH_3$ | $(C_2H_5)_2N$ | $CH_3$ | H | $2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$ | - |
| 89 | $OCH_3$ | $(C_2H_5)_2N$ | $CH_3$ | H | $2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$ | - |
| 90 | $OCH_3$ | $(C_2H_5)_2N$ | $CH_3$ | H | $2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl | - |
| 91 | $CH_3$ | $(C_2H_5)_2CH$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 92 | OH | $(C_2H_5)_2CH$ | H | $CH_3$ | $2,4\text{-}Cl_2\text{-}C_6H_3$ | 227-228 |
| 93 | $C_2H_5$ | $(C_2H_5)_2CH$ | $OCH_3$ | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 94 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | $OCH_3$ | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 95 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 96 | $C_2H_5$ | $CH_3(c\text{-}C_3H_5)CH$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |

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|---|---|---|---|---|---|---|
| 97 | $C_2H_5$ | $CH_3(c\text{-}C_4H_7)CH$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 98 | $C_2H_5$ | $(c\text{-}C_3H_5)_2CH$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 99 | $C_2H_5$ | $C_2H_5(c\text{-}C_3H_5)CH$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 100 | $C_2H_5$ | $CH_3(c\text{-}C_4H_7)CH$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 101 | $C_2H_5$ | $(HOCH_2)_2(CH_3)C$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 102 | $C_2H_5$ | $(HOCH_2)_2(CH_3)C$ | H | H | $2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$ | - |
| 103 | $C_2H_5$ | $(HOCH_2)_2(CH_3)C$ | H | H | $2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$ | - |
| 104 | $C_2H_5$ | $(HOCH_2)_2(CH_3)C$ | H | H | $2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$ | - |
| 105 | $C_2H_5$ | $(HOCH_2)_2(CH_3)C$ | H | H | $2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl | - |
| 106 | $C_2H_5$ | $(HOCH_2)_2(CH_3)C$ | H | H | $2,4\text{-}Cl_2\text{-}5\text{-}F\text{-}C_6H_2$ | - |
| 107 | $C_2H_5$ | $(HOCH_2)_2(CH_3)C$ | H | H | $2\text{-}Cl\text{-}4\text{-}OCH_3\text{-}5\text{-}F$ | - |
| 108 | $C_2H_5$ | $(HOCH_2)_2(CH_3)C$ | H | H | $2\text{-}Cl\text{-}4,5\text{-}(OCH_3)_2$ | - |
| 109 | $C_2H_5$ | $(CH_3OCH_2)_2(CH_3)C$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |
| 110 | $C_2H_5$ | $(CH_3OCH_2)_2(CH_3)C$ | H | H | $2\text{-}Cl\text{-}4\text{-}CH_3O\text{-}C_6H_3$ | - |
| 111 | $C_2H_5$ | $(CH_3OCH_2)_2(CH_3)C$ | H | H | $2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$ | - |
| 112 | $C_2H_5$ | $(CH_3OCH_2)_2(CH_3)C$ | H | H | $2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$ | - |
| 113 | $C_2H_5$ | $(CH_3OCH_2)_2(CH_3)C$ | H | H | $2\text{-}(CH_3)_2N\text{-}4\text{-}CH_3$-pyridin-5-yl | - |
| 114 | $C_2H_5$ | $(CH_3OCH_2)_2(CH_3)C$ | H | H | $2,4\text{-}Cl_2\text{-}5\text{-}F\text{-}C_6H_2$ | - |
| 115 | $C_2H_5$ | $(CH_3OCH_2)_2(CH_3)C$ | H | H | $2\text{-}Cl\text{-}4\text{-}OCH_3\text{-}5\text{-}F$ | - |
| 116 | $C_2H_5$ | $(CH_3OCH_2)_2(CH_3)C$ | H | H | $2\text{-}Cl\text{-}4,5\text{-}(OCH_3)_2$ | - |
| 117 | $C_2H_5$ | $(H_2C{=}CH)_2(CH_3)C$ | H | H | $2,4\text{-}Cl_2\text{-}C_6H_3$ | - |

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|---|---|---|---|---|---|---|
| 118 | $C_2H_5$ | $(H_2C=CH)_2(CH_3)C$ | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 119 | $C_2H_5$ | $(H_2C=CH)_2(CH_3)C$ | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 120 | $C_2H_5$ | $(H_2C=CH)_2(CH_3)C$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 121 | $C_2H_5$ | $(H_2C=CH)_2(CH_3)C$ | H | H | 2-$(CH_3)_2N$-4-$CH_3$-pyridin-5-yl | - |
| 122 | $C_2H_5$ | $(H_2C=CH)_2(CH_3)C$ | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | - |
| 123 | $C_2H_5$ | $(H_2C=CH)_2(CH_3)C$ | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 124 | $C_2H_5$ | $(H_2C=CH)_2(CH_3)C$ | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 125 | $C_2H_5$ | $(c\text{-}C_3H_5)_2(CH_3)C$ | H | H | 2,4-$Cl_2$-$C_6H_3$ | - |
| 126 | $C_2H_5$ | $(c\text{-}C_3H_5)_2(CH_3)C$ | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 127 | $C_2H_5$ | $(c\text{-}C_3H_5)_2(CH_3)C$ | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 128 | $C_2H_5$ | $(c\text{-}C_3H_5)_2(CH_3)C$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 129 | $C_2H_5$ | $(c\text{-}C_3H_5)_2(CH_3)C$ | H | H | 2-$(CH_3)_2N$-4-$CH_3$-pyridin-5-yl | - |
| 130 | $C_2H_5$ | $(c\text{-}C_3H_5)_2(CH_3)C$ | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | - |
| 131 | $C_2H_5$ | $(c\text{-}C_3H_5)_2(CH_3)C$ | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 132 | $C_2H_5$ | $(c\text{-}C_3H_5)_2(CH_3)C$ | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 133 | $C_2H_5$ | $(C_2H_5)_2(OH)C$ | H | H | 2,4-$Cl_2$-$C_6H_3$ | - |
| 134 | $C_2H_5$ | $(C_2H_5)_2(OH)C$ | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 135 | $C_2H_5$ | $(C_2H_5)_2(OH)C$ | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 136 | $C_2H_5$ | $(C_2H_5)_2(OH)C$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 137 | $C_2H_5$ | $(C_2H_5)_2(OH)C$ | H | H | 2-$(CH_3)_2N$-4-$CH_3$-pyridin-5-yl | - |
| 138 | $C_2H_5$ | $(C_2H_5)_2(OH)C$ | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | - |

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|---|---|---|---|---|---|---|
| 139 | $C_2H_5$ | $(C_2H_5)_2(OH)C$ | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 140 | $C_2H_5$ | $(C_2H_5)_2(OH)C$ | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 141 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2,4-$Cl_2$-$C_6H_3$ | |
| 142 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 143 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 144 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 145 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2-$(CH_3)_2N$-4-$CH_3$-pyridin-5-yl | - |
| 146 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | - |
| 147 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 148 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 149 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | oil |
| 150 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 151 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 152 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | - |
| 153 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 154 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 155 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | oil[g] |
| 156 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 157 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 158 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | - |
| 159 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 160 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 161 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 162 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 163 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 164 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | 2-$(CH_3)_2N$-4-$CH_3$-pyridin-5-yl | - |
| 165 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | - |
| 166 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 167 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 168 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2-$CH_3$-4-$OCH_3$-5- | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| 169 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 170 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 171 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 172 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 173 | $OCH_3$ | $(C_2H_5)_2N$ | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 174 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 175 | $OCH_3$ | $C_3H_7(CH_3)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 176 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 177 | $OCH_3$ | $C_2H_5(OCH_3)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 178 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 179 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 180 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 181 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 182 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 183 | $OCH_3$ | $(C_2H_5)_2N$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 184 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 185 | $OCH_3$ | $C_3H_7(CH_3)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 186 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 187 | $OCH_3$ | $C_2H_5(OCH_3)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 188 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2-$CH_3$-4-Cl-$C_6H_3$ | - |
| 189 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2-$CH_3$-4-Cl-$C_6H_3$ | - |
| 190 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-$CH_3$-4-Cl-$C_6H_3$ | - |
| 191 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-$CH_3$-4-Cl-$C_6H_3$ | - |

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| | | | | | | |
|---|---|---|---|---|---|---|
| 192 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | $2-CH_3-4-Cl-C_6H_3$ | - |
| 193 | $OCH_3$ | $(C_2H_5)_2N$ | H | H | $2-CH_3-4-Cl-C_6H_3$ | - |
| 194 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | $2-CH_3-4-Cl-C_6H_3$ | - |
| 195 | $OCH_3$ | $C_3H_7(CH_3)CH$ | H | H | $2-CH_3-4-Cl-C_6H_3$ | - |
| 196 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | $2-CH_3-4-Cl-C_6H_3$ | - |
| 197 | $OCH_3$ | $C_2H_5(OCH_3)CH$ | H | H | $2-CH_3-4-Cl-C_6H_3$ | - |
| 198 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2,4-Cl_2-C_6H_3$ | oil[h] |
| 199 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-Cl-4-CH_3O-C_6H_3$ | - |
| 200 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2,4,6-(CH_3)_3-C_6H_2$ | - |
| 201 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2,4,6-(OCH_3)_3-C_6H_2$ | - |
| 202 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-(CH_3)_2N-4-CH_3-$ pyridin-5-yl | - |
| 203 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2,4,6-(OCH_3)_3-C_6H_2$ | - |
| 204 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2,4-Cl_2-5-F-C_6H_2$ | - |
| 205 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-Cl-4-OCH_3-5-F$ | - |
| 206 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-Cl-4,5-(OCH_3)_2$ | - |
| 207 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-CH_3-4-OCH_3-5-F-C_6H_2$ | - |
| 208 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-CH_3-4-OCH_3-C_6H_3$ | - |
| 209 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-CH_3-4-Cl-C_6H_3$ | - |
| 210 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2,4-Cl_2-C_6H_3$ | - |
| 211 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-Cl-4-CH_3O-C_6H_3$ | - |
| 212 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2,4,6-(CH_3)_3-C_6H_2$ | - |
| 213 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2,4,6-(OCH_3)_3-C_6H_2$ | - |
| 214 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-(CH_3)_2N-4-CH_3-$ pyridin-5-yl | - |
| 215 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2,4,6-(OCH_3)_3-C_6H_2$ | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| 216 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2,4-Cl_2-5-F-C_6H_2$ | - |
| 217 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-Cl-4-OCH_3-5-F$ | - |
| 218 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-Cl-4,5-(OCH_3)_2$ | - |
| 219 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-CH_3-4-OCH_3-5-F-C_6H_2$ | - |
| 220 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-CH_3-4-OCH_3-C_6H_3$ | - |
| 221 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | $2-CH_3-4-Cl-C_6H_3$ | - |
| 222 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2,4-Cl_2-C_6H_3$ | - |
| 223 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2-Cl-4-CH_3O-C_6H_3$ | - |
| 224 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2,4,6-(CH_3)_3-C_6H_2$ | - |
| 225 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2,4,6-(OCH_3)_3-C_6H_2$ | - |
| 226 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2-(CH_3)_2N-4-CH_3-$ pyridin-5-yl | - |
| 227 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2,4,6-(OCH_3)_3-C_6H_2$ | - |
| 228 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2,4-Cl_2-5-F-C_6H_2$ | - |
| 229 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2-Cl-4-OCH_3-5-F$ | - |
| 230 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2-Cl-4,5-(OCH_3)_2$ | - |
| 231 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2-CH_3-4-OCH_3-5-F-C_6H_2$ | - |
| 232 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2-CH_3-4-OCH_3-C_6H_3$ | - |
| 233 | $C_2H_5$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2-CH_3-4-Cl-C_6H_3$ | - |
| 234 | $OCH_3$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2,4-Cl_2-C_6H_3$ | - |
| 235 | $OCH_3$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2-Cl-4-CH_3O-C_6H_3$ | - |
| 236 | $OCH_3$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2,4,6-(CH_3)_3-C_6H_2$ | - |
| 237 | $OCH_3$ | $C_2H_5OCH_2(CH_3)CH$ | H | H | $2,4,6-(OCH_3)_3-C_6H_2$ | - |
| 238 | $OCH_3$ | $C_2H_5OCH_2(CH_3)C$ | H | H | $2-(CH_3)_2N-4-CH_3-$ | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | H | | | pyridin-5-yl | |
| 239 | $OCH_3$ | $C_2H_5OCH_2(CH_3)C$ H | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 240 | $OCH_3$ | $C_2H_5OCH_2(CH_3)C$ H | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | - |
| 241 | $OCH_3$ | $C_2H_5OCH_2(CH_3)C$ H | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 242 | $OCH_3$ | $C_2H_5OCH_2(CH_3)C$ H | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 243 | $OCH_3$ | $C_2H_5OCH_2(CH_3)C$ H | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 244 | $OCH_3$ | $C_2H_5OCH_2(CH_3)C$ H | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 245 | $OCH_3$ | $C_2H_5OCH_2(CH_3)C$ H | H | H | 2-$CH_3$-4-Cl-$C_6H_3$ | - |
| 246 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2,4-$Cl_2$-$C_6H_3$ | - |
| 247 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 248 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |
| 249 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 250 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2-$(CH_3)_2N$-4-$CH_3$-pyridin-5-yl | - |
| 251 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 252 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | - |
| 253 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 254 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 255 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 256 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 257 | $C_2H_5$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2-$CH_3$-4-Cl-$C_6H_3$ | - |
| 258 | $OCH_3$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2,4-$Cl_2$-$C_6H_3$ | - |
| 259 | $OCH_3$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2-Cl-4-$CH_3O$-$C_6H_3$ | - |
| 260 | $OCH_3$ | $CH_3OCH_2(C_2H_5)C$ H | H | H | 2,4,6-$(CH_3)_3$-$C_6H_2$ | - |

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|---|---|---|---|---|---|---|
| 261 | $OCH_3$ | $CH_3OCH_2(C_2H_5)CH$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 262 | $OCH_3$ | $CH_3OCH_2(C_2H_5)CH$ | H | H | 2-$(CH_3)_2N$-4-$CH_3$-pyridin-5-yl | - |
| 263 | $OCH_3$ | $CH_3OCH_2(C_2H_5)CH$ | H | H | 2,4,6-$(OCH_3)_3$-$C_6H_2$ | - |
| 264 | $OCH_3$ | $CH_3OCH_2(C_2H_5)CH$ | H | H | 2,4-$Cl_2$-5-F-$C_6H_2$ | - |
| 265 | $OCH_3$ | $CH_3OCH_2(C_2H_5)CH$ | H | H | 2-Cl-4-$OCH_3$-5-F | - |
| 266 | $OCH_3$ | $CH_3OCH_2(C_2H_5)CH$ | H | H | 2-Cl-4,5-$(OCH_3)_2$ | - |
| 267 | $OCH_3$ | $CH_3OCH_2(C_2H_5)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-5-F-$C_6H_2$ | - |
| 268 | $OCH_3$ | $CH_3OCH_2(C_2H_5)CH$ | H | H | 2-$CH_3$-4-$OCH_3$-$C_6H_3$ | - |
| 269 | $OCH_3$ | $CH_3OCH_2(C_2H_5)CH$ | H | H | 2-$CH_3$-4-Cl-$C_6H_3$ | - |
| 270 | $C_2H_5$ | $(C_2H_5)_2CH$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | oil[i] |
| 271 | $OCH_3$ | $(C_2H_5)_2CH$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |
| 272 | $C_2H_5$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |
| 273 | $OCH_3$ | $C_4H_9(C_2H_5)CH$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |
| 274 | $C_2H_5$ | $(C_2H_5)_2N$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |
| 275 | $OCH_3$ | $(C_2H_5)_2N$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |
| 276 | $C_2H_5$ | $C_3H_7(CH_3)CH$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |
| 277 | $OCH_3$ | $C_3H_7(CH_3)CH$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |
| 278 | $C_2H_5$ | $C_2H_5(OCH_3)CH$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |
| 279 | $OCH_3$ | $C_2H_5(OCH_3)CH$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |
| 280 | $C_2H_5$ | $CH_3OCH_2(CH_3)CH$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |
| 281 | $OCH_3$ | $CH_3OCH_2(CH_3)CH$ | H | H | 2-Cl-4-$CF_3$-$C_6H_3$ | - |

Key:

a) Spectral data for Example 1: $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.38 (1H, d, J = 4.1 Hz), 7.58 (1H, d, J = 2.0 Hz), 7.55 (1H, d, J = 8.2 Hz), 7.41 (1H, dd, J = 8.2, 2.0 Hz), 6.65 (1H, d, J = 4.1 Hz), 2.79 (2H, q, J = 7.7 Hz), 2.78-2.68

(1H, m), 2.03-1.79 (4H, m), 1.25 (3H, t, J = 7.7 Hz), 0.83 (6H, t, J = 7.3 Hz). MS ($NH_3$-CI): m/e 367 (2), 366 (11), 365 (15), 364 (65), 363 (25), 362 (100). Analysis calc'd for $C_{19}H_{21}Cl_2N_3$: C, 62.99; H, 5.84; N, 11.60; found: C, 62.97; H, 5.74; N, 11.49.

b) Spectral data for Example 3: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.36 (1H, d, J = 5.0 Hz), 7.00 (2H, s), 6.50 (1H, d, J = 5.0 Hz), 2.77 (2H, q, J = 7.7 Hz), 2.76-2.66 (1H, m), 2.36 (3H, s), 2.02 (6H, s), 2.00-1.80 (4H, m), 1.21 (3H, t, J = 7.7 Hz), 0.83 (6H, t, J = 7.5 Hz). MS ($NH_3$-CI): m/e 338 (3), 337 (24), 336 (100). Analysis calc'd for $C_{22}H_{29}N_3$: C, 78.76; H, 8.71; N, 12.53; found: C, 78.74; H, 8.74; N, 12.41.

c) Spectral data for Example 16: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.39 (1H, d, J = 4.2 Hz), 7.59 (1H, d, J = 8.3 Hz), 7.58 (1H, d, J = 2.0 Hz), 7.42 (1H, dd, J = 8.3, 2.0 Hz), 6.65 (1H, d, J = 4.2 Hz), 2.82-2.72 (1H, m), 2.79 (2H, q, J = 7.3 Hz), 2.00-1.77 (4H, m), 1.35-1.10 (4H, m), 1.25 (3H, t, J = 7.3 Hz), 0.83 (3H, t, J = 7.0 Hz), 0.82 (3H, t, J = 7.5 Hz). MS ($NH_3$-CI): m/e calculated for $C_{21}H_{26}Cl_2N_3$: 390.1504, found 390.1502; 395 (3), 394 (12), 393 (17), 392 (67), 391 (29), 390 (100).

d) Spectral data for Example 18: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.36 (1H, d, J = 4.0 Hz), 7.00 (2H, s), 6.50 (1H, d, J = 4.0 Hz), 2.82-2.73 (1H, m), 2.77 (2H, q, J = 7.6 Hz), 2.36 (3H, s), 2.02 (3H, s), 2.01 (3H, s), 2.00-1.78 (4H, m), 1.38-1.09 (4H, m), 1.20 (3H, t, J = 7.6 Hz), 0.83 (3H, t, J = 7.0 Hz), 0.81 (3H, t, J = 7.3 Hz). MS ($NH_3$-CI): m/e calc'd for $C_{24}H_{34}N_3$: 364.2753, found 364.2754; 366 (4), 365 (27), 364 (100).

e) Spectral data for Example 31: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.38 (1H, d, J = 4.0 Hz), 7.58 (1H, d, J = 1.8 Hz), 7.56 (1H, d, J = 8.4 Hz), 7.42 (1H, dd, J = 8.4, 1.8 Hz), 6.65

(1H, d, J = 4.0 Hz), 3.27 (4H, q, J = 7.3 Hz), 2.80 (2H, q, J = 7.3 Hz), 1.26 (3H, t, J = 7.3 Hz), 1.00 (6H, t, J = 7.3 Hz). MS ($NH_3$-CI): calculated for $C_{18}H_{21}Cl_2N_4$: 363.1143, found 363.1146; m/e 367 (6), 366 (14), 365 (81), 364 (28), 363 (100).

f) Spectral data for Example 51: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.27 (1H, s), 7.60 (1H, d, J = 2.2 Hz), 7.43 (1H, dd, J = 8.0, 2.0 Hz), 7.32 (1H, d, J = 8.0 Hz), 3.84 (3H, s), 2.80-2.70 (1H, m), 2.08 (3H, s), 1.86-1.70 (4H, m), 0.82 (6H, t, J = 7.4 Hz). MS ($NH_3$-CI): m/e 383 (2), 382 (12), 381 (14), 380 (65), 379 (25), 378 (100).

g) Spectral data for Example 155: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.39 (1H, d, J = 4.0 Hz), 7.63 (1H, d, J = 6.6 Hz), 7.48 (1H, d, J = 8.8 Hz), 6.67 (1H, d, J = 4.0 Hz), 2.79 (2H, q, J = 7.4 Hz), 2.78-2.68 (1H, m), 2.03-1.79 (4H, m), 1.26 (3H, t, J = 7.4 Hz), 0.83 (6H, t, J = 7.5 Hz). MS ($NH_3$-CI): m/e 384 (11), 383 (16), 382 (79), 381 (20), 380 (100).

h) Spectral data for Example 198: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.40 (1H, d, J = 4.0 Hz), 7.58 (1H, d, J = 1.8 Hz), 7.55 (1H, d, J = 8.4 Hz), 7.41 (1H, dd, J = 8.4, 1.8 Hz), 6.67 (1H, d, J = 4.0 Hz), 3.79 (2H, d, J = 7.3 Hz), 3.38 (3H, s), 3.37 (1H, m), 2.82 (2H, q, J = 7.3 Hz), 1.47 (3H, d, J = 7.0 Hz), 1.25 (3H, t, J = 7.3 Hz). Mass Spectrum (AP-CI): m/e 364 (100), 366 (65), 368 (12.5). High resolution mass spectrum: for $C_{18}H_20C_{12}N_3O$ m/e calculated: 364.0984, observed 364.0988.

i) Spectral data for Example 270: TLC $R_F$ 0.19 (5:95 ethyl acetate-hexane). $^1$H NMR (300 MHz, $CDCl_3$): δ 8.42 (1H, d, J = 4.4 Hz), 7.84 (1H, br s), 7.76 (1H, d, J = 8.1 Hz), 7.69 (1H, d, J = 8.1 Hz), 6.68 (1H, d, J = 4.4 Hz), 2.79 (2H, q, J = 7.7 Hz), 2.78-2.68 (1H, m), 2.02-1.80 (4H, m), 1.25 (3H, t, J = 7.7 Hz), 0.84 (6H, t, J = 7.5 Hz).

MS ($NH_3$-CI): m/e 399 (7), 398 (33), 397 (25), 396 (100). Analysis calc'd for $C_{20}H_{21}ClF_3N_3$: C, 60.68; H, 5.36; N, 10.62; found: C, 60.66; H, 5.15; N, 10.48.

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Additional Examples of Compounds Made According to the Above-Described Synthetic Scheme and Examples

7-(2,4-dichloro-5-fluorophenyl)-2-ethyl-3-(2-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-6-methyl-3-(2-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2-chloro-4-methoxyphenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine-3-carboxaldehyde

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxyethyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-ethyl-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-ethylpyrazolo[1,5-a]pyrimidine

2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(3-pentyl)-pyrazolo[1,5-a]pyrimidine

2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(2-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dimethylphenyl)-2-ethyl-3-(2-pentyl)-pyrazolo[1,5-

a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-5-methylthio-3-(2-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(6-methyl-5-hepten-2-yl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-4-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine

7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine

7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine

7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine

7-(2,4-dimethylphenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine

4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidinyl)pentanoic acid

4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidinyl)-N-methylpentanamide

3-(5-(benzoxazol-2-ylthio)-2-pentyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine

3-(5-(benzoxazolidinethione-3-yl)-2-pentyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-2-propyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-3-(1-ethoxy-2-propyl)-2-ethyl-pyrazolo[1,5-a]pyrimidine

3-(1-acetoxy-2-propyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine

3-(1-acetoxy-2-butyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-3-butyl)pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-methoxy-3-butyl)pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-6-methyl-pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(3-heptyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-6-methyl-pyrazolo[1,5-a]pyrimidine

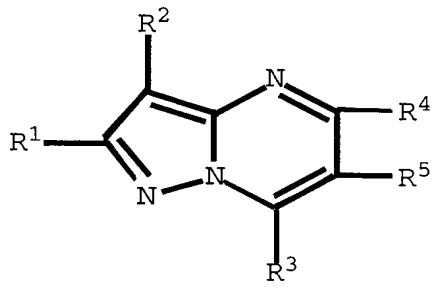
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine

Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

WHAT IS CLAIMED IS:

1. A compound of formula I:



(I)

or a stereoisomer or pharmaceutically accetable salt thereof, wherein:

$R^1$ is selected from the group consisting of
$C_{1-6}$ alkyl,
$C_{2-10}$ alkenyl,
$C_{2-10}$ alkynyl,
$C_{3-6}$ cycloalkyl,
$C_{1-6}$ alkyloxy,
$C_{1-6}$ alkyl$S(O)_n$,
$-NR^{1a}R^{1B}$ wherein $R^{1a}$ and $R^{1b}$ are independently selected from H, $C_{1-4}$ alkyl, $-C(O)C_{1-4}$alkyl,
$-C(O)NR^{1a}R^{1b}$,
$-O-C(O)C_{1-4}$alkyl,
$-XR^{1c}$ wherein $R^{1c}$ is selected from H or $-C_{1-4}$ alkylaryl;
X is selected from 0 or $S(O)_n$,
wherein $R^1$ is substituted with 0-6 substituents selected from halogen, $C_{1-4}$ alkyl, $C_{1-6}$ alkyloxy, $C_{1-4}$ haloalkyl, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

$R^2$ is selected from the group consisting of
$C_{1-10}$ alkyl,
$C_{2-10}$ alkenyl,

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$C_{2-10}$ alkynyl,

$C_{3-8}$ cycloalkyl,

$C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl,

$C_{1-10}$ alkyloxy,

$C_{1-10}$ alkyloxy$C_{1-10}$ alkyl,

$-SO_2-C_{1-10}$alkyl

$-SO_2R^{2a}$ wherein $R^{2a}$ is aryl,

$-SO_2R^{2b}$ wherein $R^{2b}$ is heteroaryl,

$-NR^{2C}R^{2D}$ wherein $R^{2c}$ and $R^{2d}$ are independently selected from H, $C_{1-8}$ alkyl, $S(O)_nC_{1-4}$alkyl, $C(O)NR^{2c}R^{2d}$, $CO_2C_{1-4}$alkyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $-C(O)C_{1-4}$alkyl or $R^{2c}$ and $R^{2d}$ may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,

- halogen,

-CN,

-C(O)L wherein L is selected from $NR^{2c}R^{2d}$, $C_{1-6}$ alkyl, H, $-OC_{1-6}$ alkyl, $O(CH_2)_mOC_{1-6}$alkyl, $O(CH_2)_mNR^{2c}R^{2d}$ , -OH, aryl, heteroaryl or $C(O)OC_{1-6}$ alkyl wherein m is 1-3;

n is 0, 1 or 2;

$R^2$ is substituted with 0-3 substituents independently selected from R', R", R"' wherein R', R" and R"' are independently selected from $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, hydroxy$C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{1-6}$ alkyloxy, hydroxy; or

$R^2$ is substituted with 0-3 substitutents independently selected from

halogen,

-CN,

$-S(O)_nR^{2e}$ wherein $R^{2e}$ is selected from $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl;

$-COR^{2f}$ wherein $R^{2f}$ is selected from H, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, and $C_{3-6}$ cycloalkyl$C_{1-4}$ alkyl;

$-CO_2R^{2f}$,

$-NR^{2g}COR^{2f}$ wherein $R^{2g}$ is selected from H, $C_{1-6}$ alkyl, $C_{3-7}$ c-alkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, wherein $R^{2h}$ is selected from H, $C_{1-6}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl and $C_{3-6}$ cycloalkyl$C_{1-6}$ alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

$C_{3-8}$ cycloalkyl wherein 0-1 carbon atoms in the $C_{4-8}$ cycloalkyl is replaced by a group selected from $-O-$, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$, and $-NSO_2R^{2e}$; and wherein $N_4$ in 1-piperazinyl is substituted with 0-1 substituents selected from $R^{2g}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$; or

the group $R^{2i}$, $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{2l}$ and in wich 0-1 carbons of $C_{4-8}$

cycloalkyl is replaced by -O-, wherein

$R^{2i}$ is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl, each $R^{2i}$ being substituted with 0-1 $OR^{2m}$ and 0-5 substituents independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{20}R^{2p}$, $-NR^{2g}CO_2R^{2n}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$;

$R^{2j}$ is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted on any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$;

$R^{2k}$ is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for $R^{2j}$, each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $-OR^{2m}$,

-SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group $R^{2f}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$;

wherein

$R^{21}$ is H, $C_{1-4}$ alkyl, $C_{3-6}$ cycloalky-$C_{1-4}$ alkyl and $C_{3-8}$ cycloalkyl;

$R^{2m}$ is H, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl, $C_{1-2}$ alkyloxy $C_{1-2}$ alkyl, $C_{1-4}$ haloalkyl, $R^{2q}S(0)_n$-$C_{1-4}$ alkyl and $R^{2r}R^{2s}N$-$C_{2-4}$ alkyl;

$R^{2n}$ is H, $C_{1-6}$ alkyl, $C_{3-10}$ cyloalkyl, $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkyl, $C_{1-2}$ alkyloxy $C_{1-2}$ alkyl, and $C_{1-4}$ haloalkyl;

$R^{2o}$ and $R^{2p}$ are independently selected at each occurrence from H, $C_{1-6}$ alkyl, $C_{3-10}$ cycloalkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl and $C_{1-4}$ haloalkyl;

$R^{2q}$ is selected from $C_{1-6}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{3-6}$ cycloalkyl- $C_{1-6}$ alkyl, aryl, aryl($C_{1-4}$ alkyl), heteroaryl and heleroaryl ($C_{1-4}$ alkyl)- and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group $C_{1-4}$ alkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy $C_{1-4}$ haloalkoxy, and dimethylamino;

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein $N_4$ in

1-piperiazinyl is substituted with 0-1 substituents selected from the group $R^{2t}$, $CO_2R^{2q}$, $COR^{2q}$ and $SO_2R^{2q}$;

$R^{2t}$ is selected from H, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy $-C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{3-6}$ cycloalkyl - $C_{1-6}$ alkyl, aryl, aryl ($C_{1-4}$ alkyl)-, heteroaryl and heteroaryl ($C_{1-4}$ alkyl);

$R^3$ is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, methylenedioxy, $C_{1-4}$ alkyloxy-$C_{1-4}$ alkyloxy, $-OR^{2m}$, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy, Br, Cl, F, I, -CN, dimethylamino, $CF_3$, $C_2F_5$, $OCF_3$, $SO_2Me$ and acetyl;

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substitued at 0-4 carbon atoms with a substituent independently selected at

each occurrence from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, F, I, $C_{1-4}$ haloalkyl, -CN, $NR^{2g}R^{2h}$, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, $COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{3a}$, $COR^{3a}$ and $SO_2R^{3a}$ wherein,

$R^{3a}$ is selected from the group $C_{1-6}$ alkyl, $C_{1-4}$ cycloalkyl-$C_{1-6}$ alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group $C_{1-4}$ alkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy, $C_{1-4}$ haloalkoxy, and dimethylamino;

$R^4$ and $R^5$ are independently selected at each occurrence from H, Br, Cl, F, I, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyloxy, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylsulfinyl, $C_{1-6}$ alkylsulfonyl, amino, $C_{1-4}$ alkylamino, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of $C_{1-7}$ alkyl, $C_{3-8}$ cycloalkyl, Br, Cl, F, I, -C(O)H, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy, $C_{1-4}$ haloalkoxy, $C_{1-4}$ alkylthio, $C_{1-4}$ alkylsulfinyl, $C_{1-4}$ alkylsulfonyl, $C_{1-6}$ alkylamino and $(C_{1-4}$ alkyl$)_2$ amino and wherein $R^4$ and $R^5$ non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, $-OC_{1-6}$-alkyl and $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{3-7}$ c-alkyl, $C_{1-6}$ alkyl$(OH)_nCO_2R$ wherein R is H or $C_{1-6}$ alkyl, $C_{1-6}$ alkyl$(OH)_n$ ,wherein n is 0-3 or $R^4$ and $R^5$ may join together to form a $C_{3-6}$ alkylene chain; with the proviso that the compounds of Formula I with $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ as specifically defined below are excluded:

(a) a compound of formula I wherein $R^1$ is unsubstituted, unbranched (linear) $C_{1-3}$ alkyl and $R^2$ is -C(O)-Ph;

(b) a compound of formula I, wherein $R^5$ is H or $C_{1-3}$ alkyl and $R^3$ is pyridyl, pyridyl-N-oxide, thien-3-yl or furan-3-yl or $C_{1-3}$ alkyl substituted versions thereof and $R^1$ is carboamoyl or unsubstituted, unbranched $C_{1-3}$ alkyl, $R^2$ is F, Cl, Br, formyl, carboxyl, CN, hydroxymethyl, unsubstituted, unbranched $C_{1-3}$ alkyl, -C(O)R, -C(O)OR, -$CH_2$OR, -C(O)O$(CH_2)_2$OR, -C(O)O$(CH_2)_2$NHR, or -C(O)O$(CH_2)_2NR^2$ wherein R is $C_{1-3}$ alkyl;

(c) a compound of formula I, wherein $R^1$ is unsubstituted, unbranched $C_{1-3}$ alkyl and $R^2$ is halogen, CN or -C(O)R wherein R is H, $C_{1-3}$ alkyl or $C_{1-4}$ alkoxy, $R^3$ is Ph substituted with $NR^{2g}C(O)R^{2m}$ ;

(d) a compound of formula I, $R^2$ is CN, halogen, $CO_2$R with R equal to $C_{1-3}$ alkyl, unsubstituted, unbranched $C_{1-3}$ alkyl, $C_{1-3}$ haloalkyl or $CONH_2$ and $R^1$ is equal to OR, SR wherein R is $C_{1-3}$ alkyl, $C_{1-4}$ haloalkyl or $C_{3-4}$ halocycloalkyl, and $R^3$ is phenyl or substituted phenyl;

(e) a compound of formula I, wherein $R^5$ is H or $C_{1-3}$ alkyl; $R^3$ is phenyl, ortho-trifluoromethylphenyl, meta-trifluorophenyl or meta-methoxyphenyl; $R^1$ is carbamoyl or unsubstituted, unbranched $C_{1-3}$ alkyl; $R^2$ is halogen, formyl, carboxyl, cyano, hydroxymethyl, unsubstituted, unbranched $C_{1-3}$ alkyl, -C(O)R, -C(O)OR, $CH_2$OR, -C(O)O$(CH_2)_2$OR, -C(O)O$(CH_2)_2$NHR or -C(O)O$(CH_2)_2NR^2$ wherein R is $C_{1-3}$ alkyl;

(g) in a compound of formula I, $R^2$ is CN, $R^1$ is methyl, $R^4$ and $R^5$ are H, $R^3$ is phenyl substituted with imidazo (or 2-methylimidazo) through the imidazo nitrogen atom;

(h) in a compound of formula I, $R^2$ is CN, $R^1$ is $SCH_3$, $R^3$ is para-chlorophenyl, $R^4$ is $SCH_3$ and $R^5$ is H;

(i) in a compound of formula I, $R^2$ is CN, $R^1$ is $SCH_3$, $R^3$ is pyrid-4-yl, $R^4$ is $SCH_3$ and $R^5$ is H ;

(j) in a compound of formula I, $R^2$ is CN, $R^1$ is $SCH_3$, $R^3$ is Ph, $R^4$ is $SCH_3$ and $R^5$ is H ;

(k) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $SCH_3$, $R^3$ is pyrid-3-yl, $R^4$ is $SCH_3$ and $R^5$ is H ;

(l) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $SCH_3$, $R^3$ is Ph, $R^4$ is $SCH_3$ (or Ph) and $R^5$ is H ;

(m) in a compound of formula I, $R^2$ is C(O)OEt, $R^1$ is $SCH_3$, $R^3$ is Ph, $R^4$ is $SCH_3$ (or Ph) and $R^5$ is H ;

(n) in a compound of formula I, $R^1$ is $N(C(O)CH_3)_2$, $R^2$ is $CH_2Ph$(p-Me, p-Cl), $R^3$ is Ph (p-ClPh), $R^4$ is $SCH_3$ and $R^5$ is H;

(o) in a compound of formula I, $R^1$ is $N(C(O)CH_3)_2$, $R^2$ is $CH_2Ph$(p-OMe), $R^3$ is p-ClPh, $R^4$ is $SCH_3$ and $R^5$ is H ;

(p) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is Ph, $R^4$ is H and $R^5$ is H;

(q) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $CH_3$, $R^3$ is Ph, $R^4$ is $CH_3$ and $R^5$ is H;

(s) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $CH_3$, $R^3$ is pyrid-4-yl, $R^4$ and $R^5$ are H;

(t) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $CH_3$, $R^3$ is m-$CF_3$Ph, $R^4$ and $R^5$ are H ;

(u) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is Ph, $R^4$ is $CH_3$ and $R^5$ is H ;

(v) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is pyrid-4-yl, $R^4$ and $R^5$ are H ;

(x) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)O$-iPr;

(y) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)O$-nPr;

(z) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)OMe$;

(aa) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)OH$;

(bb) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is $-CH_2OH$ ;

(cc) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is $-C(O)H$;

(dd) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is $-CH=CH-C(O)H$ ;

(ee) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)OEt$;

(ff) in a compound of formula I, $R^2$ is $CH_3$, $R^1$ is $CH_3$, $R^3$ is p-F-Ph, $R^4$ is c-propyl and $R^5$ is CH=CH-$CH(OH)CH_2CH(OH)CH_2C(O)O^-Na^+$;

(gg) in a compound of formula I, $R^2$ is CN, $R^1$ is $CF_3$, $R^3$ is m-Cl-Ph, $R^4$ is $CH_3$ and $R^5$ is H;

(hh) in a compound of formula I, $R^2$ is CN, $R^1$ is $CF_3$, $R^3$ is $m\text{-}CF_3\text{-}Ph$, $R^4$ is $CH_3$ and $R^5$ is H;

(ii) in a compound of formula I, $R^2$ is CN, $R^1$ is $CF_3$, $R^3$ is Ph, $R^4$ is $CH_3$ and $R^5$ is H;

(nn) in a compound of formula I, $R^2$ is $-C(O)NH_2$, $R^1$ is Me, $R^3$ is Ph, $R^4$ is H and $R^5$ is Me;

(oo) in a compound of formula I, $R^2$ is CN, $R^1$ is Me, $R^3$ is Ph, $R^4$ is H and $R^5$ is Me;

(pp) in a compound of formula I, $R^2$ is CN, $R^1$ is Me, $R^3$ is o-Cl,m-Cl-Ph, $R^4$ is H and $R^5$ is H;

(qq) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $CH_3$, $R^3$ is Ph, $R^4$ and $R^5$ are H ;

(rr) in a compound of formula I, $R^2$ is $C(O)NH_2$, $R^1$ is $CH_3$, $R^3$ is 0-CL,m-Cl-Ph, $R^4$ and $R^5$ are H ;

(ss) in a compound of formula I, $R^2$ is C(O)OMe, $R^1$ is $-SCH_2$-Ph, $R^3$ is Ph, $R^4$ is Me and $R^5$ is H ;

(tt) in a compound of formula I, $R^2$ is C(O)OMe, $R^1$ is $-SCH_2$-Ph, $R^3$ is Ph, $R^4$ is H and $R^5$ is H ;

(uu) in a compound of formula I, $R^2$ is C(O)Ph, $R^1$ is Me, $R^3$ is pyrid-4-yl, $R^4$ and $R^5$ are H ;

(vv) in a compound of formula I, $R^2$ is C(O)Ph, $R^1$ is Me, $R^3$ is m-$CF_3$-Ph, $R^4$ and $R^5$ are H ;

(ww) in a compound of formula I, $R^2$ is C(O)Ph, $R^1$ is Me, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H

(xx) in a compound of formula I, $R^2$ is CN, $R^1$ is $SCH_3$, $R^3$ is Ph, $R^4$ is Ph and $R^5$ is H ;

(yy) in a compound of formula I, $R^2$ is CN, $R^1$ is $SCH_3$, $R^3$ is Ph, $R^4$ is Ph and $R^5$ is H ;

(zz) in a compound of formula I, $R^2$ is Cl, $R^1$ is Et, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H ;

(aaa) in a compound of formula I, $R^2$ is $CO_2H$, $R^1$ is Et, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H;

(bbb) in a compound of formula I, $R^2$ is $CO_2H$, $R^1$ is $CH_3$, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H and H Cl salt ;

(ccc) in a compound of formula I, $R^2$ is C(O)OEt, $R^1$ is $CH_3$, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H ;

(ddd) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is pyrid-3-yl, $R^4$ is H and $R^5$ is $CH_3$ ;

(eee) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H ;

(fff) in a compound of formula I, $R^2$ is C(O)OEt, $R^1$ is Et, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H ;

(ggg) in a compound of formula I, $R^2$ is CN, $R^1$ is Et, $R^3$ is pyrid-3-yl, $R^4$ and $R^5$ are H ;

(hhh) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_3$, $R^3$ is m-$CF_3$Ph, $R^4$ and $R^5$ are H ;

(iii) in a compound of formula I, $R^2$ is CN, $R^1$ is $CH_2CN$, $R^3$ is m-$CF_3$-Ph, $R^4$ and $R^5$ are H ;

(jjj) in a compound of formula I, $R^2$ is C(O)OMe, $R^1$ is Me, $R^3$ is m-$CF_3$-Ph, $R^4$ and $R^5$ are H ;

(kkk) in a compound of formula I, $R^2$ is CN, $R^1$ is Et, $R^3$ is m-OMe-Ph, $R^4$ and $R^5$ are H ;

(lll) in a compound of formula I, $R^2$ is C(O)OEt, $R^1$ is Et, $R^3$ is Ph, $R^4$ and $R^5$ are H ;

(mmm) in a compound of formula I, $R^2$ is C(O)OEt, $R^1$ is Et, $R^3$ is m-$CF_3$-Ph, $R^4$ and $R^5$ are H ;

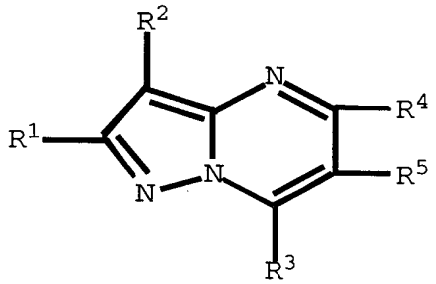
(nnn) in a compound of formula I, $R^2$ is CN, $R^1$ is Et, $R^3$ is m-$CF_3$-Ph, $R^4$ is H and $R^5$ is $CH_3$ ;

(ooo) in a compound of formula I, $R^2$ is CN, $R^1$ is Et, $R^3$ is m-$CF_3$, $R^4$ and $R^5$ are H ;

(ppp) in a compound of formula I, $R^2$ is CN, $R^1$ is $C(O)NH_2$, $R^3$ is m-$CF_3$-Ph, $R^4$ and $R^5$ are H ;

(qqq) in a compound of formula I, $R^2$ is CN, $R^1$ is Et, $R^3$ is Ph, $R^4$ and $R^5$ are H.

2. A compound of formula I:




(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

$R^1$ is selected from the group consisting of

$C_{1-6}$ alkyl,

$C_{2-10}$ alkenyl,

$C_{2-10}$ alkynyl,

$C_{3-6}$ cycloalkyl,

$C_{1-6}$ alkyloxy,

$C_{1-6}$ alkyl$S(O)_n$,

$-NR^{1a}R^{1B}$ wherein $R^{1a}$ and $R^{1b}$ are independently selected from H, $C_{1-4}$ alkyl, $-C(O)C_{1-4}$alkyl, $-C(O)NR^{1a}R^{1b}$, $-O-C(O)C_{1-4}$alkyl,

$-XR^{1c}$ wherein $R^{1c}$ is selected from H or $-C_{1-4}$ alkylaryl;

X is selected from 0 or $S(O)_n$,

wherein $R^1$ is substituted with 0-6 substituents selected from halogen, $C_{1-4}$ alkyl, $C_{1-6}$ alkyloxy, $C_{1-4}$ haloalkyl, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

$R^2$ is selected from the group consisting of

$C_{1-10}$ alkyl excluding unsubstituted, unbranched $C_{1-3}$alkyl,

$C_{2-10}$ alkenyl,

$C_{2-10}$ alkynyl,

$C_{3-8}$ cycloalkyl,

$C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl,

$C_{1-10}$ alkyloxy,

$C_{1-10}$ alkyloxy$C_{1-10}$ alkyl,

$C_{1-4}$ alkoxy $C_{1-4}$ alkyl,

$-SO_2-C_{1-10}$alkyl

$-SO_2R^{2a}$ wherein $R^{2a}$ is aryl,

$-SO_2R^{2b}$ wherein $R^{2b}$ is heteroaryl,

$-NR^{2C}R^{2D}$ wherein $R^{2c}$ and $R^{2d}$ are independently selected from H, $C_{1-8}$ alkyl, $S(O)_nC_{1-4}$ alkyl, $C(O)NR^{2c}R^{2d}$, $CO_2C_{1-4}$alkyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $-C(O)C_{1-4}$alkyl

or $R^{2c}$ and $R^{2d}$ may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,

n is 0, 1 or 2;

$R^2$ is substituted with 0-3 substituents independently selected from R', R", R"' wherein R', R" and R"' are independently selected from $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, hydroxy$C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{1-6}$ alkyloxy, hydroxy, or

$R^2$ is substituted with 0-3 substituents independently selected from:

-CN,

$-S(O)_nR^{2e}$ wherein $R^{2e}$ is selected from $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl;

$-COR^{2f}$ wherein $R^{2f}$ is selected from H, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, and $C_{3-6}$ cycloalkyl$C_{1-4}$ alkyl;

$-CO_2R^{2f}$,

$-NR^{2g}COR^{2f}$ wherein $R^{2g}$ is selected from H, $C_{1-6}$ alkyl, $C_{3-7}$ c-alkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, wherein $R^{2h}$ is selected from H, $C_{1-6}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl and $C_{3-6}$ cycloalkyl$C_{1-6}$ alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

$C_{3-8}$ cycloalkyl wherein 0-1 carbon atoms in the $C_{4-8}$ cycloalkyl is replaced by a group selected from -O-, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$, and $-NSO_2R^{2e}$; and wherein $N_4$ in 1-piperazinyl is substituted with 0-1 substituents selected from $R^{2g}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$; or

the group $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{2l}$ and in wich 0-1 carbons of $C_{4-8}$ cycloalkyl is replaced by -O-, wherein

$R^{2j}$ is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted

on any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$;

$R^{2k}$ is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for $R^{2j}$, each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group $R^{2f}$, $CO_2R^{2e}$, $COR^{2e}$ and $SO_2R^{2e}$;

wherein

$R^{2l}$ is H, $C_{1-4}$ alkyl, $C_{3-6}$ cycloalky-$C_{1-4}$ alkyl and $C_{3-8}$ cycloalkyl;

$R^{2m}$ is H, $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl, $C_{1-2}$ alkyloxy $C_{1-2}$ alkyl, $C_{1-4}$ haloalkyl, $R^{2q}S(0)_n$-$C_{1-4}$ alkyl and $R^{2r}R^{2s}N$-$C_{2-4}$ alkyl;

$R^{2n}$ is H, $C_{1-6}$ alkyl, $C_{3-10}$ cyloalkyl, $C_{3-6}$ cycloalkyl-$C_{1-6}$ alkyl, $C_{1-2}$ alkyloxy $C_{1-2}$ alkyl, and $C_{1-4}$ haloalkyl;

$R^{2o}$ and $R^{2p}$ are independently selected at each occurrence from H, $C_{1-6}$ alkyl, $C_{3-10}$ cycloalkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl and $C_{1-4}$ haloalkyl;

$R^{2q}$ is selected from $C_{1-6}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{3-6}$ cycloalkyl- $C_{1-6}$ alkyl, aryl, aryl($C_{1-4}$ alkyl), heteroaryl and heleroaryl ($C_{1-4}$ alkyl)-

and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group $C_{1-4}$ alkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy $C_{1-4}$ haloalkoxy, and dimethylamino;

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein $N_4$ in 1-piperiazinyl is substituted with 0-1 substituents selected from the group $R^{2t}$, $CO_2R^{2q}$, $COR^{2q}$ and $SO_2R^{2q}$;

$R^{2t}$ is selected from H, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ alkoxy $-C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{3-6}$ cycloalkyl - $C_{1-6}$ alkyl, aryl, aryl ($C_{1-4}$ alkyl)-, heteroaryl and heteroaryl ($C_{1-4}$ alkyl);

$R^3$ is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, methylenedioxy, $C_{1-4}$ alkyloxy-$C_{1-4}$ alkyloxy, $-OR^{2m}$, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, $-NO_2$, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy, Br, Cl, F, I, -CN, dimethylamino, $CF_3$, $C_2F_5$, $OCF_3$, $SO_2Me$ and acetyl;

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl,

benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substitued at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, F, I, $C_{1-4}$ haloalkyl, -CN, $NR^{2g}R^{2h}$, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, $COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{3a}$, $COR^{3a}$ and $SO_2R^{3a}$ wherein,

$R^{3a}$ is selected from the group $C_{1-6}$ alkyl, $C_{1-4}$ cycloalkyl-$C_{1-6}$ alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group $C_{1-4}$ alkyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy, $C_{1-4}$ haloalkoxy, and dimethylamino;

$R^4$ and $R^5$ are independently selected at each occurrence from H, Br, Cl, F, I, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyloxy, $C_{1-6}$ alkylthio, $C_{1-6}$ alkylsulfinyl, $C_{1-6}$ alkylsulfonyl, amino, $C_{1-4}$ alkylamino, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of $C_{1-7}$ alkyl, $C_{3-8}$ cycloalkyl, Br, Cl, F, I, -C(O)H, $C_{1-4}$ haloalkyl, nitro, $C_{1-4}$ alkoxy, $C_{1-4}$ haloalkoxy, $C_{1-4}$ alkylthio, $C_{1-4}$ alkylsulfinyl, $C_{1-4}$ alkylsulfonyl, $C_{1-6}$ alkylamino and $(C_{1-4}$ alkyl$)_2$ amino and wherein $R^4$ and $R^5$ non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, $-OC_{1-6}$-alkyl and $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{3-7}$ c-alkyl, $C_{1-6}$

alkyl$(OH)_nCO_2R$ wherein R is H or $C_{1-6}$ alkyl, $C_{1-6}$ alkyl$(OH)_n$ ,wherein n is 0-3 or $R^4$ and $R^5$ may join together to form a $C_{3-6}$ alkylene chain.

3. The compound according to Claim 1 or 2 wherein

$R^1$ is selected from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, $-XR^{1c}$ wherein $R^1$ is substituted with 0-6 substituents selected from halogen, $C_{1-4}$ alkyl or $C_{1-4}$ haloalkyl;

$R^2$ is selected from substituted-$C_{1-10}$ alkyl, branched $C_{3-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, $C_{3-8}$ cycloalkyl, $C_{3-6}$ cycloalkyl $C_{1-6}$ alkyl, $-NR^{2c}R^{2d}$ wherein, in the case of substituted-$C_{1-10}$ alkyl, 1-3 substitutents are independently selected from the group $R^{2i}$, $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{21}$ and in wich 0-1 carbons of $C_{4-8}$ cycloalkyl is replaced by -O- and wherein the $R^2$ groups, other than substituted-$C_{1-10}$ alkyl, are substituted with 0-3 substituents independently selected from the group $R^{2i}$, $R^{2j}$, $R^{2k}$, $C_{1-6}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, Br, Cl, F, I, $C_{1-4}$ haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl$OR^{2g}$, and $C_{3-8}$ cycloalkyl which is substituted with 0-1 $R^{21}$ and in wich 0-1 carbons of $C_{4-8}$ cycloalkyl is replaced by -O-.

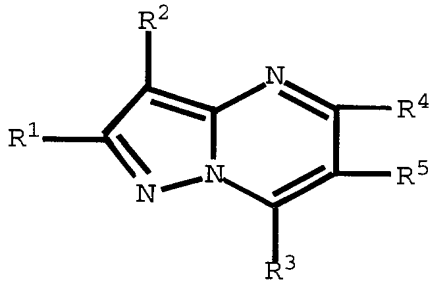
4. The compound according to Claims 1 or 2 or 3 wherein $R^3$ is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

5. The compound according to Claims 1,2,3 or 4 wherein $R^2$ is selected from $C_1$ alkyl of the formula -CR'R"R"' wherein R', R" and R"' are independently selected from H, $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, hydroxy$C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy$C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{1-6}$ alkyloxy, hydroxy, with the proviso that each of R',R" and R'" cannot be H;

or $R^2$ is selected from $NR^{2c}R^{2d}$ wherein $R^{2c}$ and $R^{2d}$ are independently selected from H or $C_{1-6}$ alkyl.

6. The compound according to Claims 1-5 wherein $R^3$ is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom wherein, aryl is phenyl, each phenyl being substituted with 0-5 substituents independently selected at each occurrence from $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, methylenedioxy, $C_{1-4}$ alkyloxy-$C_{1-4}$ alkyloxy, $-OR^{2m}$, Br, Cl, F, I, $C_{1-4}$ haloalkyl, -CN, $-NO_2$, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy, Br, Cl, F, I, -CN, dimethylamino, $CF_3$, $C_2F_5$, $OCF_3$, $SO_2Me$ and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substitued at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group $C_{1-6}$ alkyl, $C_{3-6}$ cycloalkyl, Br, F, I, $C_{1-4}$ haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, $COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each pyridyl being substituted at any nitrogen atom with 0-1 substituents selected from the group $R^{2g}$, $CO_2R^{3a}$, $COR^{3a}$ and $SO_2R^{3a}$ .

7. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein

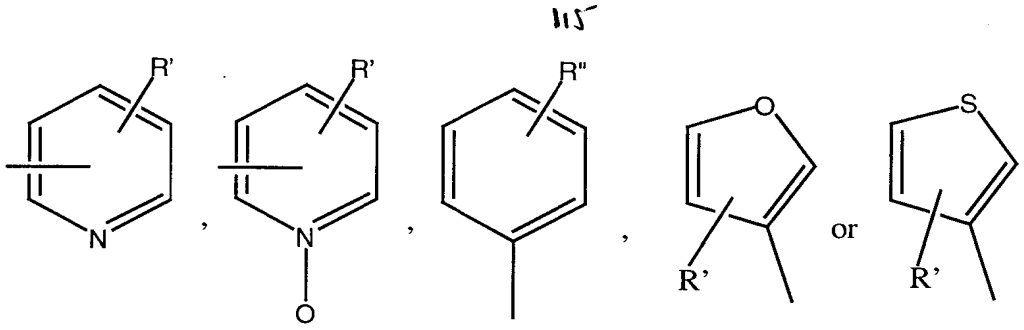
$R^1$ is selected from $C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy, -SH or OH;

$R^2$ is selected from $C_{1-4}$ alkyl which is unsubstituted or substituted with 1-4 substitutents selected from $C_{1-6}$ alkyl, $C_{3-8}$ cycloalkyl, $C_{1-6}$ alkyl$OR^{2g}$, $C_{2-6}$ alkenyl or $OR^{2g}$ wherein $R^{2g}$ is H or $C_{1-6}$ alkyl;

$R^3$ is selected from an aryl or heteroaryl group bonded through an unsaturated carbon atom that is unsubstituted or substituted with 1-4 substituents selected from Cl, F, I, Br, -OH, $CF_3$, $S(O)_nC_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $C_{1-6}$ alkyl or $NR^{2g}R^{2h}$ wherein $R^{2g}$ and $R^{2h}$ are independently selected from H or $C_{1-6}$ alkyl;

$R^4$ and $R^5$ are independently selected from H, $C_{1-6}$ alkyl or $C_{1-6}$ alkyloxy,

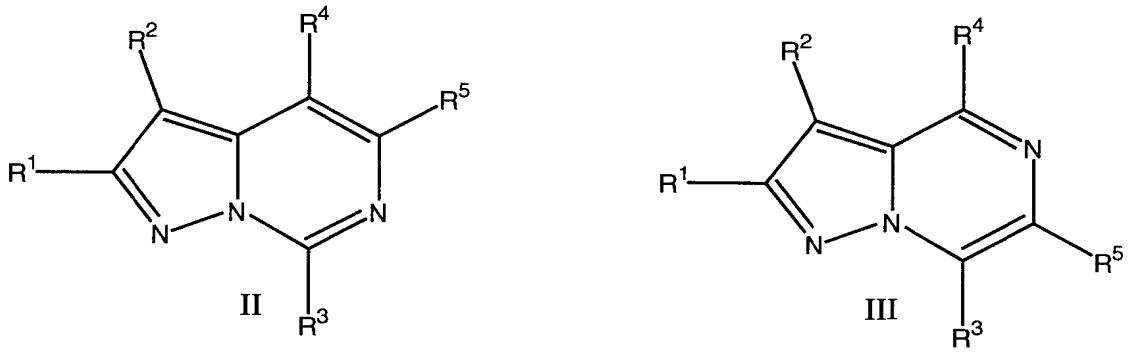
with the proviso that when $R^1$ and $R^2$ are unsubstituted, unbranched $C_{1-3}$ alkyl, $R^3$ may not be



wherein R' is H or $C_{1-3}$ alkyl and R" is H or o-trifluoromethyl, m-trifluoromethyl or m-methoxy.

8. The compound according to Claims 1-7 wherein $R^3$ is substituted with 2-4 substituents.

9. A compound of the formula:



or a pharmaceutically acceptable salt or isomer thereof wherein $R^1$-$R^5$ and other variables are as defined in claims 1-8.

10. Use of a compound according to Claims 1-9 in therapy.

11. Use of a compound according to Claims 1-9 to antagonize a CRF-1 receptor in mammals including humans wherein binding to the receptor causes and ultimately

results in the treatment of affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of according to Claims 1-9.

12. A pharmaceutical composition comprising a compound according to Claims 1-9 and a pharmaceutically acceptable carrier with the proviso that, in a compound of formula I according to Claim 1, proviso (d) compounds are not excluded.

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## (54) CRF1 RECEPTOR ANTAGONIST, PHARMACEUTICAL FORMULATIONS AND SOLID FORMS THEREOF FOR THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA

(57) Provided are methods related to treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine (Formula I), or a pharmaceutically acceptable salt thereof. Further provided are pharmaceutical formulations and solid forms of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and their use in the treatment of congenital adrenal hyperplasia (CAH).

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## Description

### TECHNICAL FIELD

**[0001]** The present disclosure relates to 4-(2-chloro-4-methoxy5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for the treatment of congenital adrenal hyperplasia (CAH). The present disclosure further relates to pharmaceutical formulations and solid forms of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and their use in the treatment of congenital adrenal hyperplasia (CAH).

### BACKGROUND

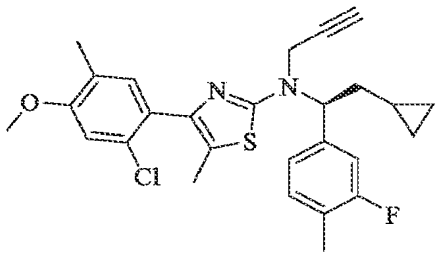
**[0002]** Classic congenital adrenal hyperplasia (CAH) is a disease that includes a group of autosomal recessive disorders that result in an enzyme deficiency that alters the production of adrenal steroids due to 21-hydroxylase deficiency, a condition that results in little or no cortisol biosynthesis. One clinical manifestation of the absence of cortisol is the lack of feedback inhibition of pituitary adrenocorticotropic hormone (ACTH) secretion. Increased ACTH levels cause adrenal hyperplasia and the enzyme mutation causes a shunting of cortisol precursor steroids to alternate pathways. Most notably, the shunting of androgens leads to virilization and other developmental complications in females and the over-accumulation of ACTH is associated with the formation of testicular adrenal rest tumors in males. In addition, since the same enzyme (21-hydroxylase) is used in the pathway for the biosynthesis of the mineralocorticoids, a number of these patients suffer from aldosterone deficiency which can result in dehydration and death due to salt-wasting. The prevalence of classic 21-hydroxylase deficiency CAH in the US general population, based on newborn screening, has been documented as 1:10,000 to 1:20,800 (Trakakis et al., "An update to 21-hydroxylase deficient congenital adrenal hyperplasia," Gynecol. Endocrinol. (2010) 26(1):63-71; Hertzberg et al., "Birth prevalence rates of newborn screening disorders in relation to screening practices in the United States," J. Pediatr. (2011) 159(4):555-560).

**[0003]** Pediatric patients from birth through adolescence, and females in particular, appear to be the most vulnerable population of CAH sufferers and represent the subgroup of patients with the greatest unmet medical need (Cheng and Speiser, "Treatment outcomes in congenital adrenal hyperplasia," Adv. Pediatr. (2012) 59(1):269-281; Merke and Poppas, "Management of adolescents with congenital adrenal hyperplasia," Lancet Diabetes Endocrinol. (2013) 1(4):341-352). Excessive androgen production in these younger patients results in early onset puberty and adrenarche, changes in skeletal maturation patterns, short stature caused by premature growth plate fusion, as well as significant hirsutism and acne problems. While survival is properly ensured through steroid replacement strategies based on physiologic dosing of glucocorticoids (e.g., hydrocortisone) and mineralocorticoids (e.g., fludrocortisone), these doses are often inadequate to suppress the accumulating ACTH and overproduction of progestogens and androgens (e.g., 17-hydroxyprogesterone [17-OHP], androstenedione, and testosterone). The uncontrolled symptoms of androgen excess, indeed, have a substantial impact on the day-to-day functioning and development of these patients.

**[0004]** Currently, exogenous corticosteroids are the standard of care for treating patients with classic CAH. This treatment is used to correct the cortisol deficiency and reduce the excessive ACTH levels and androgen excess. However, the dose and duration of steroid use required to suppress ACTH are typically well above the normal physiological level used for cortisol replacement alone (as in patients with Addison's disease). This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, reduced growth velocity, and decreased bone mineral density in CAH patients (Elnecave et al., "Bone mineral density in girls with classical congenital adrenal hyperplasia due to CYP21 deficiency," J. Pediatr. Endocrinol. Metab. (2008) 21(12):1155-1162; King et al., "Long-term corticosteroid replacement and bone mineral density in adult women with classical congenital adrenal hyperplasia," J. Clin. Endocrinol. Metab. (2006) 91(3):865-869; Migeon and Wisniewski, "Congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Growth, development, and therapeutic considerations," Endocrinol. Metab. Clin. North Am. (2001) 30(1):193-206).

**[0005]** Corticotropin releasing factor (CRF) is a hypothalamic hormone released directly into the hypophyseal portal vasculature and acts on specific corticotropin releasing factor 1 (CRF1) receptors on corticotropes in the anterior pituitary to stimulate the release of ACTH. Blockade of these receptors has been shown to decrease the release of ACTH in both animals and humans. Therefore, compounds that block CRF1 receptors have the potential to directly inhibit the excessive ACTH release that occurs in CAH and thereby allow for normalization of androgen production while using lower, more physiologic doses of hydrocortisone.

**[0006]** The compound of Formula (I)



(I)

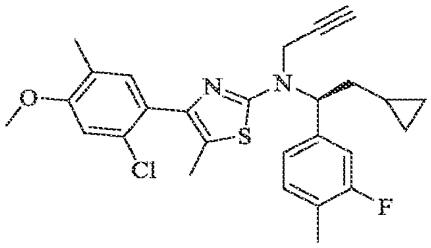
4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, is a selective CRF1 receptor antagonist. The compound of Formula (I) can be prepared according to the methods described in U.S. Patent Nos. 6,586,456 and 8,314,249, each of which is hereby incorporated by reference in its entirety. The compound of Formula (I) is a low solubility compound with low bioavailability. Partially due to its low solubility, attempts at formulating the compound of Formula (I) have proven to be difficult, particularly for formulations suitable for pediatric administration.

**[0007]** Thus, there is a need for a treatment for CAH that avoids the severe complications associated with corticosteroid therapy. There is also a need for a formulation of the compound of Formula (I) with increased bioavailability and a need for a formulation of the compound of Formula (I) that is suitable for pediatric administration. The formulations and methods of the present invention help address these and other needs.

## SUMMARY

**[0008]** Provided herein is a pharmaceutical composition comprising:

(a) a compound of Formula (I):

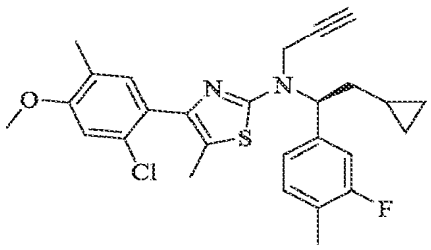


(I)

or a pharmaceutically acceptable salt thereof; and
(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

**[0009]** Provided herein is a pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):

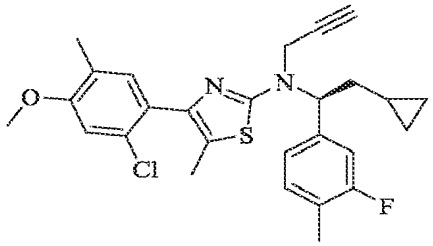


(I)

or a pharmaceutically acceptable salt thereof;
(b) one or more of a sweetener, an anti-oxidant, and a flavor; and
(c) a liquid vehicle.

**[0010]** Also provided herein is a pharmaceutical composition of the present disclosure (e.g., a pharmaceutical composition in oral solution dosage form of the present disclosure) for use in therapy, for example, for use in any of the methods disclosed herein.

**[0011]** Provided herein is a method for treating congenital adrenal hyperplasia (CAH) comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

**[0012]** Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject.

**[0013]** Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3- fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject.

**[0014]** Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

**[0015]** Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

**[0016]** Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic

hormone (ACTH); and (c) androstenedione in the subject.

**[0017]** In some embodiments, the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof. In some embodiments, the circadian release occurs between the hours of 2 a.m. and 10 a.m.

**[0018]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

**[0019]** In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25%. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50%.

**[0020]** In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50%.

**[0021]** In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

**[0022]** In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

**[0023]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

**[0024]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

**[0025]** Provided herein is a method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of androstenedione in the subject. In some embodiments, the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

**[0026]** Also provided herein is a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of androstenedione in the subject.

**[0027]** Also provided herein is use of a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of androstenedione in the subject.

**[0028]** In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

**[0029]** Provided herein is a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

**[0030]** Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

**[0031]** Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable

salt thereof, in the manufacture of a medicament for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

**[0032]** In some embodiments, the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

**[0033]** Provided herein is a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof. In some embodiments, the corticosteroid is a glucocorticoid.

**[0034]** Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

**[0035]** Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3- fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

**[0036]** Provided herein is a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

**[0037]** Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

**[0038]** Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

**[0039]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

**[0040]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

**[0041]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

**[0042]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

**[0043]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

**[0044]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

**[0045]** Provided herein is a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

**[0046]** Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(lS)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

**[0047]** Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the method comprises:

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(lS)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

**[0048]** In some embodiments, the method further comprises (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i). In some embodiments, the method further comprises (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

**[0049]** In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

**[0050]** In some embodiments, steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

**[0051]** In some embodiments, steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

**[0052]** In some embodiments, step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

**[0053]** In some embodiments, step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

**[0054]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cycloptopyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

**[0055]** Provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, where in the subject is in a fed state.

**[0056]** Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject, wherein the subject is in a fed state.

**[0057]** Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject, wherein the subject is in a fed state.

**[0058]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1500 calories per liter with a caloric distribution of about 14.7% protein, about 32% fat and about 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

**[0059]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

**[0060]** In some embodiments, administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of $C_{max}$, AUC, or combinations thereof when comparing oral administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the fed and fasting states.

**[0061]** In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10. In some embodiments, the ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state is about 5 to about 10.

**[0062]** Provided herein is a method of reducing glucocorticoid burden in a subject as measured after a time period of administration of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

**[0063]** Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing glucocorticoid burden in a subject, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

**[0064]** Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing glucocorticoid burden in a subject, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

**[0065]** Provided herein is a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

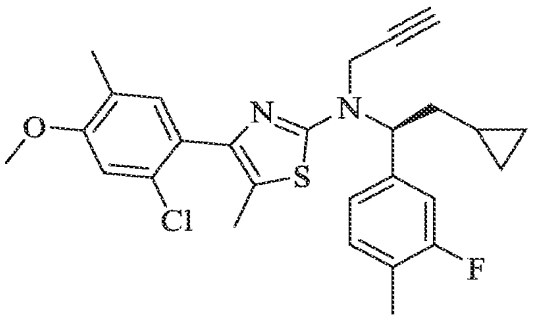
**[0066]** Also provided herein is a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

**[0067]** Also provided herein is use of a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

**[0068]** Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof for use in therapy, for example, for use in any of the methods disclosed herein.

**[0069]** Also provided herein is use of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(lS)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods disclosed herein.

**[0070]** Also provided herein is a spray-dried dispersion containing 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



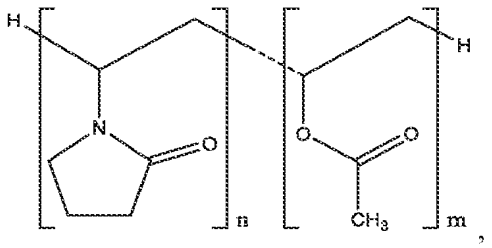
(I)

or a pharmaceutically acceptable salt thereof, and a polymer. In some embodiments, the polymer is selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:9 to about 1:1.

**[0071]** In some embodiments, the polymer is a neutral polymer. In some embodiment, the neutral polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

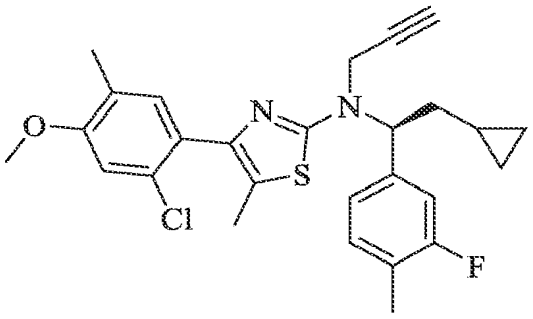
**[0072]** In some embodiments, the polymer is an enteric polymer. In some embodiments, the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer.

**[0073]** In some embodiments, the polymer is a pyrrolidone polymer. In some embodiments, the pyrrolidone polymer is selected from polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone vinyl acetate (PVP/VA). In some embodiments, the pyrrolidone polymer is PVP/VA. In some embodiments, the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 40:60 to about 60:40 by weight. In some embodiments, the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight. In some embodiments, the copolymer has the structure:



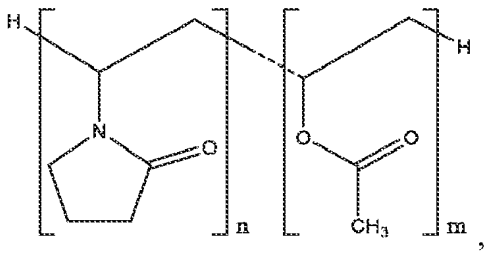
wherein the value of n is about 1 to about 2 times the value of m. In some embodiments, the copolymer is copovidone, wherein the value of n is about 1.16 times the value of m. In some embodiments, the copolymer is copovidone having an average molecular weight of about 45,000 to about 70,000.

**[0074]** Provided herein is a spray-dried dispersion comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



wherein the value of n is about 1 to about 2 times the value of m and the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight; and wherein the weight ratio of the compound of Formula (I) to the copolymer is from about 1:1 to about 1:9.

**[0075]** In some embodiments of the spray-dried dispersions of the present disclosure, the compound of Formula (I) and the polymer together form homogeneous particles. In some embodiments, the particles have a particle size distribution $D_{50}$ of about 5 μm to about 100 μm. In some embodiments, the particles have a particle size distribution $D_{50}$ of about 10 μm to about 50 μm. In some embodiments, the particles have a particle size distribution $D_{50}$ of about 15 μm to about 30 μm.

**[0076]** In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:1.5 to about 1:9. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:2.5 to about 1:4. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is about 1:3.

**[0077]** In some embodiments, the particles have a residual solvent content less than about 2 wt %. In some embodiments, the particles have a residual solvent content less than about 1 wt %. In some embodiments, the particles have a residual solvent content of about 0.5 wt % or less.

**[0078]** In some embodiments, the compound of Formula (I) in the dispersion is substantially amorphous.

**[0079]** Also provided herein is a method for preparing a spray-dried dispersion of the present disclosure, comprising: dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer.

**[0080]** In some embodiments, the method comprises removing the organic solvent after formation of the spray-dried dispersion by drying the spray-dried dispersion. In some embodiments, the spray-dried dispersion is dried with a convection tray dryer. In some embodiments, the organic solvent is acetone.

**[0081]** In some embodiments, the spray dryer inlet temperature is about 60°C to about 80°C. In some embodiments, the spray dryer inlet temperature is about 72°C.

**[0082]** In some embodiments, the spray dryer outlet temperature is about 25°C to about 45°C. In some embodiments, the spray dryer outlet temperature is about 35°C.

**[0083]** In some embodiments, the homogeneous particles comprise a bulk density of less than about 0.2 g/mL. In some embodiments, the homogeneous particles comprise a bulk density of less than about 0.15 g/mL.

**[0084]** In some embodiments, the homogeneous particles comprise a tapped density of less than about 0.3 g/mL. In some embodiments, the homogeneous particles comprise a tapped density of less than about 0.25 g/mL.

**[0085]** Also provided herein is a pharmaceutical composition comprising the spray-dried dispersion of the present disclosure and one or more pharmaceutically acceptable excipients. In some embodiments, the spray-dried dispersion is present in an amount of about 20% to about 90% w/w of the composition. In some embodiments, the spray-dried dispersion is present in an amount of about 40% to 80% w/w of the composition.

**[0086]** In some embodiments, the pharmaceutical excipients are selected from the group consisting of a filler, a lubricant, and combinations thereof. In some embodiments, the filler is selected from the group consisting of a binder, a diluent, a disintegrant, a glidant, a surfactant, and combinations thereof.

**[0087]** In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg.

**[0088]** In some embodiments, the pharmaceutical composition is formulated as a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film. In some

embodiments, the pharmaceutical composition is in tablet form. In some embodiments, the pharmaceutical composition is in capsule form. In some embodiments, the pharmaceutical composition is coated.

**[0089]** In some embodiments, the spray-dried dispersion is formulated for oral administration and exhibits a positive food effect when administered orally. In some embodiments, the spray-dried dispersion has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10. In some embodiments, wherein the spray-dried dispersion has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 5 to about 10.

**[0090]** Also provided herein is a method for preparing a pharmaceutical composition, comprising combining the spray-dried dispersion of the present disclosure with one or more pharmaceutically acceptable excipients.

**[0091]** Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure.

**[0092]** Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

**[0093]** Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

**[0094]** In some embodiments, the spray-dried dispersion or the pharmaceutical composition is administered to the subject in a fed state. In some embodiments, the spray-dried dispersion or the pharmaceutical composition is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than 30%. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the spray-dried dispersion or the pharmaceutical composition.

**[0095]** In some embodiments, administering the spray-dried dispersion or the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of $C_{max}$, AUC, or combinations thereof when comparing oral administration of the spray-dried dispersion or pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10. In some embodiments, the ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 10 to about 20. In some embodiments, the ratio of the Cmax in the fed state to the $C_{max}$ in the fasted state is about 10 to about 20.

**[0096]** In some embodiments of the disclosed methods, the subject is a pediatric subject.

**[0097]** Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in therapy, for example, for use in any of the methods disclosed herein.

**[0098]** Also provided herein is use of a spray-dried dispersion of the present disclosure for manufacture of a medicament for use in any of the methods disclosed herein.

**[0099]** Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0100]** Also provided herein is a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

**[0101]** Also provided herein is use of pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

**[0102]** Also provided herein is pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy, for example, for use in any of the methods disclosed herein.

**[0103]** Also provided herein is use of pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods disclosed herein.

**[0104]** Also provided herein is a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, comprising orally administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared

as a spray-dried dispersion.

**[0105]** Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

**[0106]** Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

**[0107]** In some embodiments, the subject is a pediatric subject.

**[0108]** Also provided herein is a method of improving oral bioavailability of a compound of Formula (I) in a subject, comprising orally administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

**[0109]** Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in a method of improving oral bioavailability of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

**[0110]** Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of improving oral bioavailability of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

**[0111]** In some embodiments, the subject is a pediatric subject.

**[0112]** Also provided herein is a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

**[0113]** Also provided herein is a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt, for use in therapy, for example, for use in any of the methods disclosed herein.

**[0114]** Also provided herein is use of a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt, for manufacture of a medicament for use in any of the methods disclosed herein.

**[0115]** Other features and advantages of the methods, processes, formulations, and uses provided herein will be apparent from the following detailed description and figures, and from the claims.

## DESCRIPTION OF DRAWINGS

**[0116]**

FIG. 1 shows the dissolution performance of several spray-dried dispersion formulations in 0.5 wt% simulated intestinal fluid (SIF) in phosphate buffered saline (PBS), pH 6.5.

FIG. 2 shows the vertical membrane flux cell integrated in the μDiss Profiler™ used for the membrane flux assay.

FIG. 3 shows non-sink dissolution data for several spray-dried dispersion formulations and the compound of Formula (I) in 0.5 wt% SIF in PBS, pH 6.5.

FIG. 4 is a graph showing membrane flux of 1 mg/mL GB/IB 0.5 wt% SIF doses of the compound of Formula (I) and various spray-dried dispersion formulations over time. The solid lines indicate flux ($\mu g\ min^{-1}\ cm^{-2}$) and the broken lines indicate concentration (μg/mL) in 0.5% SIF.

FIG. 5 is a flow diagram of the spray drying manufacturing process used to prepare a 1000 g batch of a SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64.

FIGS. 6A and 6B are line graphs showing the pharmacokinetic results of a bioavailability and food effect study in dogs. FIG. 6A shows the results from Cohort 1 and FIG. 6B shows the results from Cohort 2.

FIG. 7 is a flow chart showing the study design of a Phase 1 study of the pharmacokinetics and food effect of the compound of Formula (I) in healthy adult subjects.

FIGS. 8A and 8B are line graphs showing the mean plasma concentration versus time profiles for the compound of Formula (I) under fasted and fed conditions, respectively, in healthy adult subjects.

FIGS. 9A-9C are spaghetti plots of the pharmacokinetics of the compound of Formula (I) in healthy adult subjects under fasted and fed conditions. FIG. 9A shows the $AUC_{0\text{-tlast}}$ values. FIG. 9B shows the $AUC_{0\text{-}\infty}$ values. FIG. 9C shows the $C_{max}$ values.

FIG. 10 is a flow chart showing the study design of a Phase 1 study of the bioavailability, pharmacokinetics and food effect of the compound of Formula (I) in healthy adult subjects.

FIG. 11 shows the study design of a Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia.

FIGs. 12A and 12B show the arithmetic mean values for adrenocorticotropic hormone (ACTH) (FIG. 12A) and 17-hydroxyprogesterone (17-OHP) (FIG. 12B) for all 8 Cohort 1 subjects plotted at each time point for pre-treatment baseline (circles), day 1 (squares), and day 14 (triangles).

FIGs. 13A and 13B show arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for pre-treatment baseline (circles), day 1 (squares), and day 14 (triangles).

FIGs. 14A and 14B show the reduction of ACTH at timepoints 8-, 10-, and 12-hours postdose. FIG 14A shows the values for each time point as compared to baseline. FIG. 14B shows the mean values across all three timepoints.

FIGs. 15A and 15B show the reduction of 17-OHP at timepoints 8-, 10-, and 12-hours postdose. FIG 15A shows the values for each time point as compared to baseline. FIG. 15B shows the mean values across all three timepoints.

FIGs. 16A and 16B show the reduction of androstenedione at timepoints 8-, 10-, and 12-hours postdose. FIG 16A shows the values for each time point as compared to baseline. FIG. 16B shows the mean values across all three timepoints.

FIG. 17A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 17B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 17C: shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 18A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 18B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 18C shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 19A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 19B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 19C shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 20 is a scheme showing the manufacturing process for forming 50 mg capsules of the compound of Formula (I).

FIG. 21 is an alternative scheme showing the manufacturing process for forming 50 mg capsules of the compound of Formula (I).

FIGs. 22A and 22B show a scheme showing the manufacturing process for forming SDD granules of the compound of Formula (I).

FIG. 23 is a scheme showing the manufacturing process for forming 50 mg/nL liquid formulation 1 of the compound of Formula (I).

FIG. 24 is a scheme showing the manufacturing process for forming 50 mg/nL liquid formulation 2 of the compound of Formula (I).

FIG. 25 is an XRPD spectrum of the compound of Formula (I) free base crystalline form I.

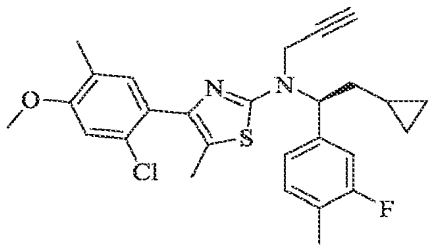
FIG. 26 is a DSC spectrum of the compound of Formula (I) free base crystalline form I.

FIG. 27 is an XRPD spectrum of the compound of Formula (1) tosylate crystalline form 1.

FIG. 28 is a DSC and TGA spectrum of the compound of Formula (I) tosylate crystalline form 1.

## DETAILED DESCRIPTION

**[0117]** As described herein, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, is a selective CRF1 receptor antagonist that has been found to be effective treating congenital adrenal hyperplasia. Specifically, the compound of Formula (I) has been found to effectively reduce several biomarkers associated with congenital adrenal hyperplasia.

**[0118]** Newborn screening for CAH is performed by immunoassay to measure 17-OHP levels in heel-stick capillary blood specimens obtained within the first 72 hours of life. The blood sample is analyzed for 17-OHP by commercially available dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA; PerkinElmer, Waltham Massachusetts) (White et al., J. Pediatr. 163:10-12 (2013)). Second-tier screening tests utilizing biochemical and molecular genetic testing methods, performed between 8 and 14 days of life, are employed by nine states in the United States and strongly recommended by an additional 5 states. The biochemical method includes immunoassay with organic solvent extraction or liquid chromatography followed by tandem mass spectrometry to measure steroid ratios of 17-OHP, androstenedione, and 21-deoxycortisol to cortisol *(see, e.g.,* Speiser et al., Int. J. Pediatr. Endocrinol. 2010:494173, 2010). The genetic screen looks for *CYP21A2* mutations that are associated with CAH. While not widely employed in the U.S., the addition of a second screening could potentially improve the sensitivity of the overall screening process, where sensitivity of the first screen alone is approximately 72%.

**[0119]** In absence of results from the newborn screening, female infants with classical CAH are typically identified due to the presence of ambiguous genitalia. Males have normal genitalia at birth and therefore are not diagnosed unless newborn screening is conducted or other medical complications come to attention. Infants who are not initially diagnosed with CAH and suffer from the salt-wasting form of the disease are later diagnosed in the setting of poor weight gain, vomiting, hyperkalemia and hyponatremia within the first few weeks of life.

**[0120]** Treatment of CAH is based on normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment include cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women and to inhibit testicular adrenal rest tumors in men. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

**[0121]** The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient cortisol is available during events that may elicit a strong stress response (e.g., intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of iatrogenic Cushing's syndrome due to glucocorticoid overtreatment in an effort to adequately suppress androgen production, or Addisonian syndrome due to under-treatment.

**[0122]** Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione, testosterone, renin activity, and electrolytes. Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, and insulin resistance *(see, e.g.,* Kim et al., Semin. Reprod. Med. 27(4):316-21 (2009)). A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the aforementioned adverse outcomes *(see, e.g.,* Finkielstain et al., J. Clin. Endocrinol Metab. 97(12):4429-38 (2012)).

**[0123]** Treatment of CAH includes efforts to normalize the cortisol deficiency with glucocorticoids (usually hydrocor-

tisone in children but often more potent agents with narrow therapeutic indices, such as dexamethasone, in adults) and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients *(see, e.g.,* Elnecave et al., J. Pediatr. Endocrinol. Metab. 21:1155-62 (2008); King et al., J. Clin. Endocrinol. Metab. 91(3):8656-59 (2006); Migeon et al., Endocrinol. Metab. Clin. North Am. 30:193-206 (2001)). Recently, best practices for the clinical management of congenital adrenal hyperplasia were published in the *Journal of Clinical Endocrinology and Metabolism* (Speiser, P.W., et al. J. Clin. Endocrinol Metab. November 2018, 103(11): 1-46). This article is incorporated by reference in its entirety.

**[0124]** Corticotropin-releasing factor (CRF) was isolated from ovine hypothalami and identified as a 41-amino acid peptide. CRF has been found to produce profound alterations in endocrine, nervous, and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotropic hormone ("ACTH"), β-endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (see, *e.g.,* Vale et al., Science 213:1394-1397,1981). Secretion of CRF causes release of ACTH from corticotrophs in the anterior pituitary via binding to the $CRF_1$ receptor, a member of the class B family of G-protein coupled receptors.

**[0125]** Due to the physiological significance of CRF, the development of biologically-active small molecules having significant $CRF_1$ receptor binding activity and which are capable of antagonizing the $CRF_1$ receptor remains a desirable goal and has been the subject of ongoing research and development for the treatment of anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse.

**[0126]** The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21-hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-hydroxyprogesterone (17-OHP). Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone causing virilization in females. In addition, 21-hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically cortisol and aldosterone. Cortisol is a critical negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

**Definitions**

**[0127]** Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

**[0128]** The term "about" preceding a value for DSC, TGA, or $T_g$, which are reported as degrees Celsius, have an allowable variability of ±5°C. In all other instances, unless otherwise specified, the term "about" preceding a stated value includes the stated value and also includes ±20% of the stated value, and includes more specifically values of ±10%, ±5%, ±2%, and ±1% of the stated value.

**[0129]** To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that when a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any range therein.

**[0130]** "Room temperature" or "RT" refers to the ambient temperature of a typical laboratory, which is typically around 25°C.

**[0131]** "Spray-drying" refers to the method of producing a dry powder from a solution or slurry. The solution or slurry is atomized or rapidly dried with a hot gas, e.g., air or nitrogen, that causes the solvent to evaporate quickly and uniformly. A "spray-dried dispersion" refers to the powder obtained from the spray-drying process.

**[0132]** The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, co-solvents, complexing agents, dispersion media, coatings, antibacterial and antifungal agents, isotonic

and absorption delaying agents, and the like, which are not biologically or otherwise undesirable. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic formulations is contemplated. Supplementary active ingredients can also be incorporated into the fonnulations. In addition, various excipients, such as are commonly used in the art, can be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (2010); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 12th Ed., The McGraw-Hill Companies.

**[0133]** "Subject," as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate. In some embodiments, the subject is a human.

**[0134]** In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having congenital adrenal hyperplasia (CAH). In some embodiments, the subject is suspected of having CAH. In some embodiments, the subject has a clinical record indicating that the subject has CAH (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein). In some embodiments, the subject is a pediatric subject.

**[0135]** The term "pediatric subject" as used herein refers to a subject under the age of 21 years at the time of diagnosis or treatment. The term "pediatric" can be further divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman et al., Textbook of Pediatrics, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph et al., Rudolph's Pediatrics, 21st Ed. New York: McGraw-Hill, 2002; and Avery et al., Pediatric Medicine, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

**[0136]** As used herein, the terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

**[0137]** The term "preventing," as used herein, means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

**[0138]** The term "administration" or "administering" refers to a method of giving a dosage of a compound or pharmaceutical formulation to a vertebrate or invertebrate, including a mammal, a bird, a fish, or an amphibian. The preferred method of administration can vary depending on various factors, e.g., the components of the pharmaceutical formulation, the site of the disease, and the severity of the disease.

**[0139]** As used herein, "therapeutically effective amount" is an amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or an amount of a pharmaceutical composition comprising the compound of Formula (I), which is sufficient to achieve the desired effect and can vary according to the nature and severity of the disease condition, and the potency of the compound. A therapeutic effect is the relief, to some extent, of one or more of the symptoms of the disease, and can include curing a disease. "Curing" means that the symptoms of active disease are eliminated. However, certain long-term or permanent effects of the disease can exist even after a cure is obtained (such as, e.g., extensive tissue damage).

**[0140]** The term "amorphous" means a solid in a solid state that is a non-crystalline state. Amorphous solids are disordered arrangements of molecules and therefore possess no distinguishable crystal lattice or unit cell and consequently have no definable long range ordering. The solid state form of a solid may be determined by polarized light microscopy, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), or other standard techniques known to those of skill in the art.

**[0141]** As used herein, "time of day window" refers to a period of time defined by a window start time and a window stop time. These times all refer to local times where a sample was taken. The phrase "same time of day window" when

referring to samples taken from the subject mean, e.g., that a sample taken at 8:15 a.m. and a sample taken at 9:15 a.m. are considered to be taken in the same time of day window of, e.g., 2 a.m. to 10 a.m. or 6 a.m. to 10 a.m.

**Methods**

**[0142]** The present disclosure relates to methods of treating congenital adrenal hyperplasia (CAH). The methods include administering to a subject a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a subject a therapeutically effective amount of a SDD of the present disclosure that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a subject a therapeutically effective amount of pharmaceutical composition of the present disclosure that contains a SDD that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0143]** Provided herein is a method of treating congenital adrenal hyperplasia (CAH) comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof to normalize or partially normalize levels of biomarkers associated with congenital adrenal hyperplasia. In some embodiments, normalizing or partially normalizing levels of biomarkers comprises reducing levels of elevated biomarkers or increasing levels of depressed biomarkers as compared to subject without CAH.

**[0144]** Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers associated with congenital adrenal hyperplasia. In some embodiments, the biomarkers are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

**[0145]** In some embodiments, the reduction in level of any of the biomarkers (e.g., any of 17-OHP, ACTH, and androstenedione) is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof. A day prior to administering the compound of Formula (I) applies to a subject that has not previously been administered the compound of Formula (I) within at least the past 24 hours.

**[0146]** In some embodiments, the circadian release of biomarkers associated with CAH occurs between the hours of 2 a.m. and 10 a.m. In other embodiments, the circadian release of biomarkers associated with CAH occurs between the hours of 6 a.m. and 10 a.m.

**[0147]** In some embodiments of any of the methods disclosed herein, the compound of Formula (I), or a pharmaceutically acceptable salt, is administered to the subject at nighttime or administration prior to sleep (i.e., bedtime administration). In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered six to eight hours prior to the circadian release of the biomarker. Administration prior to the circadian release may be adapted for shift workers (*e.g.,* those who work at night and sleep during the day), in which case administration will not necessarily occur at nighttime. Administration is therefore dependent upon the expected circadian release of the biomarker, and can vary depending upon the individual's (*i.e.*, subject, patient) particular work and sleep patterns.

**[0148]** In some embodiments of the methods provided herein, the level of 17-hydroxyprogesterone is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25%. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50%. In some embodiments of the methods provided herein, the level of 17-hydroxyprogesterone is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

**[0149]** In some embodiments, the level of 17-hydroxyprogesterone is reduced to a level within the range of 17-hydroxyprogesterone expected for a subject without CAH, i.e., less than 1,000 ng/dL or less than 200 ng/dL.

**[0150]** In some embodiments of the methods provided herein, the level of adrenocorticotropic hormone is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50%.

**[0151]** In some embodiments of the methods provided herein, the level of adrenocorticotropic hormone is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about

55% to about 90%, or about 60% to about 90% from pre-administration levels.

**[0152]** In some embodiments, the level of adrenocorticotropic hormone is reduced to a level within the range of adrenocorticotropic hormone expected for a subject without CAH.

**[0153]** In some embodiments of the methods provided herein, the level of androstenedione is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

**[0154]** In some embodiments of the methods provided herein, the level of androstenedione is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

**[0155]** In some embodiments, the level of androstenedione is reduced to a level within the range of androstenedione expected for a subject without CAH, i.e., less than 200 ng/dL.

**[0156]** Also provided herein is a method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce one or more biomarker of CAH in a subject, e.g. reduce the androstenedione in the subject. Growth impairment can refer to, e.g., accelerated height velocity, accelerated weight velocity, and/or accelerated bone age.

**[0157]** Provided herein is a method for reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

**[0158]** Provided herein is a method for reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the corticosteroid is a glucocorticoid.

**[0159]** Also provided herein is a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. The long-term effects of glucocorticoid treatment are well documented in the art (see, e.g., Oray, M. et al. (2016): Long-term effect of glucocorticoids, Expert Opinion on Drug Safety. DOI: 10.1517/14740338.2016.1140743). Such side effects are associated with every biological system, e.g., musculoskeletal (e.g., osteoporosis, avascular necrosis of bone, and myopathy), endocrine and metabolic (e.g., hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression), gastrointestinal (e.g., gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis), cardiovascular (e.g., hypertension, coronary heart disease, ischemic heart disease, heart failure), dermatologic (e.g., dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, and hair loss), neuropsychiatric (e.g., mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, and delirium), ophthalmologic (e.g., cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, and central serous chorioretinopathy), and immunologic (e.g., suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections).

**[0160]** Accordingly, in some embodiments, the side effects of glucocorticoid treatment are selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, reactivation of latent infections, and any combination thereof.

**[0161]** Provided herein is a method of treating congenital adrenal hyperplasia in a subject comprising

(i)measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
(ii)analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
(iii)administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof if the subject

is determined to have elevated levels of the one or more biomarkers.

**[0162]** In some embodiments, the method further comprises (iv) measuring the level of the one or more biomarkers after administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i). In some embodiments, the method further comprises (v) continuing the administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

**[0163]** In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

**[0164]** In some embodiments, steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

**[0165]** In some embodiments, steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

**[0166]** In some embodiments, step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

**[0167]** In some embodiments, step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

**[0168]** In some embodiments of the methods of the present disclosure, the compound of Formula (I) is administered at an amount equivalent to from about 25 mg to about 150 mg of the compound of Formula (I) free base. In some embodiments, compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at an amount equivalent to about 50 mg or about 100 mg of the compound of Formula (I) free base.

**[0169]** In some embodiments of the methods disclosed herein, compound of Formula (I) is administered in the free base form.

**[0170]** In some embodiments of the methods disclosed herein, the compound of Formula (I) is administered once daily.

**[0171]** Also provided herein is a method of treating CAH in a pediatric subject. The methods include administering to a pediatric subject a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a pediatric subject a therapeutically effective amount of a SDD of the present disclosure that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a pediatric subject a therapeutically effective amount of pharmaceutical composition of the present disclosure that contains a SDD that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pediatric subject is a neonate. In some embodiments, the pediatric subject is an infant. In some embodiments, the pediatric subject is a child. In some embodiments, the pediatric subject is an adolescent.

**[0172]** In some embodiments of the methods of the present disclosure, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject in a fed state. The term "fed state," as used herein, refers to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof from about 1 hour before consumption of food or a nutritional composition to about 1 hour after consumption of food or a nutritional composition. The term "fasted state," as used herein, refers to a gap of at least two hours between consumption of food or a nutritional composition and administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject with food or a nutritional composition, such as a nutritional supplement or formula, a meal replacement beverage, a liquid dietary supplement, or a high caloric liquid meal. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject within about 1 hour before the subject has consumed food or a nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject within about 1 hour after the subject has consumed food or a nutritional composition. Examples of suitable nutritional compositions include, but are not limited to, infant formulas, dietary supplements, dietary substitutes, and rehydration compositions. In some embodiments, the food is a product containing concentrated calories and protein. In some embodiments, the nutritional composition is a composition utilized for enteral and parenteral supplementation for infants, specialty infant formulas, supplements for the elderly, and supplements for those with gastrointestinal difficulties and/or malabsorption. Adult and pediatric nutritional formulas are well known in the art and are commercially available (e.g., Similac®, Ensure®, Jevity® and Alimentum® from Ross Products Division, Abbott Laboratories, Columbus, Ohio).

**[0173]** In some embodiments, the nutritional composition is in liquid form. The energy density of the nutritional compositions, when in liquid form, can range from about 0.6 Kcal to about 3 Kcal per mL. In some embodiments, the nutritional composition is in solid or powdered form. When in solid or powdered form, the nutritional supplements can contain from

about 1.2 to more than 9 Kcals per gram, such as about 3 to 7 Kcals per gram.

**[0174]** In some embodiments, the nutritional composition is a meal replacement bar. Examples include PowerBar®, Glucerna® bars, Choice DM® bars, Ensure® bars, and Boost® bars. In some embodiments, the nutritional composition is a nutrition shake or meal replacement beverage. Commercially available examples include the Ensure® branded adult products (such as Ensure® Original, Ensure® Plus, Ensure® Enlive, Ensure® High Protein, Ensure® Clear, and Ensure® Light), Glucerna®, Choice DM®, Slim Fast®, Pediasure®, Glytrol®, and Resource®. In some embodiments, the nutritional composition is Ensure® Plus. In some embodiments, the nutritional composition is vanilla-flavored Ensure® Plus. Ensure Plus® is a high calorie liquid dietary supplement that contains 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

**[0175]** In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

**[0176]** In some embodiments of the methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject before administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject at the same time as administration of the nutritional composition.

**[0177]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject, followed by administration of the nutritional composition. In some embodiments, the nutritional composition is administered about 1 minute, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, or about 60 minutes, or within a range defined by any of the preceding values after administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the nutritional composition is administered 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, or 60 minutes, or within a range defined by any of the preceding values after administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the nutritional composition is administered within 30 minutes of administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

**[0178]** In some embodiments, the nutritional composition is administered to the subject, followed by administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered about 1 minute, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, or about 60 minutes, or within a range defined by any of the preceding values after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, or 60 minutes, or within a range defined by any of the preceding values after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered within 30 minutes of administering the nutritional composition. In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

**[0179]** In some embodiments of the methods, a food effect is observed between administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof in a fed state versus a fasted state. The term "food effect," as used herein, refers to the relative difference in AUC (area under the curve AUC(0-t) and/or $AUC_{(0-\infty)}$) or $C_{max}$ (maximum plasma concentration or peak plasma concentration) of an active substance, when the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally to a subject, concomitantly with food or in a fed state as compared to the same values when the same compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered in a fasted state. The food effect (F) is calculated as:

$$F\% = [(X_{fasted} - X_{fed}) / X_{fasted}] \times 100$$

where $X_{fed}$ and $X_{fasted}$ are the values of AUC ($AUC_{(0-t)}$ and/or $AUC_{(0-\infty)}$) or $C_{max}$ in the fed and fasted state, respectively. In some embodiments, an increased, or positive, food effect is observed when the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to a subject in a fed state. In some embodiments, administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in an increased, or positive, food effect, whereby an increased $C_{max}$ and/or AUC are observed when administered orally in the fed state as compared to the fasting state.

**[0180]** In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10, such as about 5 to about 9, about 5 to about 8, about 5 to about 7, about 5 to about 6, about 6 to about 10, about 6 to about 9, about 6 to about 8, about 6 to about 7, about 7 to about 10, about 7 to about 9, about 7 to about 8, about 8 to about 10, about 8 to about 9, or about 8 to about 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5, about 6, about 7, about 8, about 9, or about 10, or within a range defined by any of the preceding values. In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is about 10 to about 20.

**[0181]** In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is 5 to 10, such as 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 10, 6 to 9, 6 to 8, 6 to 7, 7 to 10, 7 to 9, 7 to 8, 8 to 10, 8 to 9, or 8 to 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is 5, 6, 7, 8, 9, or 10, or within a range defined by any of the preceding values.

**[0182]** In some embodiments of the methods, the ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state is about 5 to about 10, such as about 5 to about 9, about 5 to about 8, about 5 to about 7, about 5 to about 6, about 6 to about 10, about 6 to about 9, about 6 to about 8, about 6 to about 7, about 7 to about 10, about 7 to about 9, about 7 to about 8, about 8 to about 10, about 8 to about 9, or about 8 to about 10. In some embodiments, the ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state is about 5, about 6, about 7, about 8, about 9, or about 10, or within a range defined by any of the preceding values. In some embodiments, the mean $C_{max}$ of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is about 1.5 to about 3 times higher in the fed stated compared to the fasted state. In some embodiments of the methods, the ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state is 5 to 10, such as 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 10,6 to 9, 6 to 8, 6 to 7, 7 to 10, 7 to 9, 7 to 8, 8 to 10, 8 to 9, or 8 to 10. In some embodiments, the ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state is 5, 6, 7, 8, 9, or 10, or within a range defined by any of the preceding values. In some embodiments, the mean $C_{max}$ of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is 1.5 to 3 times higher in the fed stated compared to the fasted state. In some embodiments, the mean $C_{max}$ of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is about 2 times higher in the fed stated compared to the fasted state. In some embodiments of the methods, the ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state is about 10 to about 20.

**[0183]** In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a meal. In some embodiments, the meal is a high fat, high caloric meal. In some embodiments, the meal is a low fat, low caloric meal. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered within approximately 5 minutes after the start of the meal. In some embodiments, the meal is an evening meal. In some embodiments, the meal is a morning meal.

**[0184]** In some embodiments, the fed state is with a high fat meal. In some embodiments, the fed state is with a low fat meal. The FDA has provided draft guidelines regarding high fat and low fat meals ("Assessing the Effects of Food on Drugs in INDs and NDAs - Clinical Pharmacology Considerations Guidance for Industry," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), February 2019, Clinical Pharmacology). Table 1 shows test meal definitions provided by the FDA guidance.

**Table 1**

| Meal Type | Total Kcal | Fat | | |
|---|---|---|---|---|
| | | Kcal | Grams | Percent |
| High-Fat | 800-1000 | 500-600 | 55-65 | 50 |
| Low-Fat | 400-500 | 100-125 | 11-14 | 25 |

**[0185]** The composition of a high fat meal provided by the FDA guidance is depicted in Table 2.

**Table 2. Composition of a High Fat Meal***

| | |
|---|---|
| Total Calories | 800-1000 |
| Calories from Protein | 150 |
| Calories from Carbohydrates | 250 |
| Calories from Fat | 500-600 |

(continued)

| | |
|---|---|
| An Example of a High Fat Breakfast | • Two eggs fried in butter<br>• Two strips of bacon<br>• Two slices of toast with butter<br>• Four ounces of hash brown potatoes<br>• Eight ounces of whole milk |
| *50 percent of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained. | |

**[0186]** The composition of a low fat meal provided by the FDA guidance is depicted in Table 3.

**Table 3. Composition of a Low Fat Meal**

| | |
|---|---|
| Total Calories | 400-500 |
| Fat (g) | 250 |
| Percent Calories from Fat | 25 |
| An Example of a Low Fat Breakfast* | • Eight ounces milk (1 percent fat)<br>• One boiled egg<br>• One packet flavored instant oatmeal made with water |
| *This low-fat breakfast contains 387 calories and has 10 grams of fat. | |

**[0187]** In some embodiments, a high fat meal contains 800-1000 total Kcal and 500-600 fat Kcal. In some embodiments, a low fat meal contains 400-500 total Kcal and 100-125 fat Kcal.

**[0188]** Also provided herein is a method of improving gastrointestinal absorption of a compound of Formula (I), or pharmaceutically acceptable salt thereof, in a subject. The method includes orally administering to the subject a pharmaceutical composition of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I), or pharmaceutically acceptable salt thereof, which has not been prepared as a spray-dried dispersion. In some embodiments, the subject is a pediatric subject.

**[0189]** Also provided herein is a method of improving oral bioavailability of a compound of Formula (I), or pharmaceutically acceptable salt thereof, in a subject. The method includes orally administering to the subject a pharmaceutical composition of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I), or pharmaceutically acceptable salt thereof, which has not been prepared as a spray-dried dispersion.

**[0190]** In some embodiments of the methods provided herein, the subject is a pediatric subject.

**[0191]** Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition is a lipidic semi-solid formulation. In some embodiments, the pharmaceutical composition is a liquid formulation. In some embodiments, the pharmaceutical composition is administered to the subject in a fed state.

**[0192]** Also provided herein is a pharmaceutical composition of the present disclosure for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject. In some embodiments, the subject is in a fed state.

**[0193]** In some embodiments, the pharmaceutical composition is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

**[0194]** In some embodiments, the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of $C_{max}$, AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the

fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1.5 to 3. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is 1.5 to 3.

**[0195]** In some embodiments, the subject is a pediatric subject.

**[0196]** In some embodiments, the pharmaceutical composition is formulated for oral administration and exhibits a positive food effect when administered orally. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 10 to about 20. In some embodiments, the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 10 to about 20. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 1 to about 4 or about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4. In some embodiments, the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 1 to about 4. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3. In some embodiments, the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 1.5 to about 3. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1 to 4 or 5 to 10. In some embodiments, the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of 1 to 4 or 5 to 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1 to 4. In some embodiments, the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of 1 to 4. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1.5 to 3. In some embodiments, the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of 1.5 to 3.

**[0197]** In some embodiments, the pharmaceutical composition is administered to the subject with a meal. In some embodiments, the meal is a high fat meal. In some embodiments, the meal is a low fat meal. In some embodiments, the pharmaceutical composition is administered within about 5 minutes after the start of the meal. In some embodiments, the meal is an evening meal. In some embodiments, the meal is a morning meal.

**[0198]** In some embodiments, administering the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of $C_{max}$, AUC, or combinations thereof of the compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound

of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1.5 to 3. In some embodiments, the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is 1.5 to 3.

**[0199]** For the avoidance of doubt, also provided herein is the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, or corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the corresponding methods, as described herein.

**[0200]** For the avoidance of doubt, also provided herein is use of the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

**[0201]** For the avoidance of doubt, also provided herein is use of the corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

**Reduction in glucocorticoid burden, adrenal androgens and precursors**

**[0202]** Glucocorticoids are a class of corticosteroids, which are a class of steroid hormones. Glucocorticoids are corticosteroids that bind to the glucocorticoid receptor that is present in almost every vertebrate animal cell. In some embodiments, the subject is concurrently receiving a dose of a glucocorticoid. In some embodiments, the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate. In some embodiments, the glucocorticoid is cortisol (hydrocortisone). In some embodiments, the glucocorticoid is cortisone. In some embodiments, the glucocorticoid is prednisone. In some embodiments, the glucocorticoid is dexamethasone.

**[0203]** In some embodiments, the glucocorticoid dose is measured in hydrocortisone equivalents. In some embodiments, the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents. Any glucocorticoid can be given in a dose that provides approximately the same glucocorticoid effects as normal cortisol production; this is referred to as physiologic, replacement, or maintenance dosing.

**[0204]** In some embodiments, the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m$^2$/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m$^2$/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m$^2$/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0205]** In some embodiments, the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m$^2$/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m$^2$/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m$^2$/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0206]** In some embodiments, the glucocorticoid dose concurrently given to the subject is a normal physiological dose of hydrocortisone equivalents. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 2 to about 16 mg/m$^2$/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 4 to about 12 mg/m$^2$/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 5 to about 11 mg/m$^2$/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 6 to about 10 mg/m$^2$/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 7 to about 9 mg/m$^2$/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 4 to about 9 mg/m$^2$/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 8 mg/m$^2$/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 12 mg/m$^2$/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is less than about 8 mg/m$^2$/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15 or about 16 mg/m$^2$/day, or within a range defined by any of the preceding values.

**[0207]** In some embodiments, the glucocorticoid dose concurrently given to the subject is at the upper limit of normal of a normal physiological dose of hydrocortisone equivalents. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the upper limit of normal is 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 2 times the normal physiological dose. In some embodiments, the upper limit of normal is about 2.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, or about 3.0 times the normal physiological dose, or within a range defined by any of the preceding values.

**[0208]** In some embodiments, the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the compound of Formula (I), or a

pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0209]** In some embodiments, the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0210]** In some embodiments, the glucocorticoid dose of the subject is reduced within a range defined by any of the preceding values.

**[0211]** In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In

some embodiments, the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0212]** In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0213]** In some embodiments, the level of 17-hydroxyprogesterone of the subject is reduced within a range defined by any of the preceding values.

**[0214]** In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0215]** In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0216]** In some embodiments, the level of adrenocorticotropic hormone of the subject is reduced within a range defined by any of the preceding values.

**[0217]** In some embodiments, the level of androstenedione is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration

of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0218]** In some embodiments, the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0219]** In some embodiments, the level of androstenedione of the subject is reduced within a range defined by any of the preceding values.

**[0220]** In some embodiments, the level of testosterone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0221]** In some embodiments, the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0222]** In some embodiments, the level of testosterone of the subject is reduced within a range defined by any of the preceding values.

**[0223]** In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than 1.5 times the upper limit of normal and the level of androstenedione is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0224]** In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0225]** In some embodiments, the level of 17-hydroxyprogesterone and androstenedione of the subject is reduced within a range defined by any of the preceding values.

**[0226]** In some embodiments, the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0227]** In some embodiments, the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0228]** In some embodiments, the quality of life as measured by the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) in the subject is improved after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) is relative to the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) results prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0229]** In some embodiments, fatigue is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in fatigue is relative to the fatigue prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0230]** In some embodiments, sleep is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in sleep is relative to the sleep prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0231]** In some embodiments, insulin resistance is reduced in the subject after a time period of administration of the

compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of insulin resistance is relative to the insulin resistance prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0232]** In some embodiments, glucose tolerance is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in glucose tolerance is relative to the glucose tolerance prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0233]** In some embodiments, glucose control is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in glucose control is relative to the glucose control prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0234]** In some embodiments, lipid levels reflecting dyslipidemia are reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in lipid levels is relative to the lipid levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0235]** In some embodiments, lipid levels reflecting hyperlipidemia are reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in lipid levels is relative to the lipid levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0236]** In some embodiments, bone mineral density is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in bone mineral density is relative to the bone mineral density prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0237]** In some embodiments, bone turnover is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in bone turnover is relative to the bone turnover prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0238]** In some embodiments, fat mass is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in fat mass is relative to the fat mass prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0239]** In some embodiments, body weight is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in body weight is relative to the body weight prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0240]** In some embodiments, central obesity is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in central obesity is relative to the central obesity prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0241]** In some embodiments, blood pressure is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in blood pressure is relative to the blood pressure prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0242]** In some embodiments, the severity of hirsutism is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in the severity of hirsutism is relative to the severity of hirsutism prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0243]** In some embodiments, menstrual cyclicity is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in menstrual cyclicity is relative to the menstrual cyclicity prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0244]** In some embodiments, control of testicular adrenal rest tumor is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in control of testicular adrenal rest tumor is relative to the control of testicular adrenal rest tumor prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0245]** In some embodiments, fertility is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in fertility is relative to the fertility prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0246]** In some embodiments, gonadotropin levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in gonadotropin levels is relative to the gonadotropin levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0247]** In some embodiments, progesterone levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in progesterone

levels is relative to the progesterone levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0248]** In some embodiments, semen levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in semen levels is relative to the semen levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0249]** In some embodiments, LH (luteinizing hormone) levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in LH levels are relative to the LH levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0250]** In some embodiments, the time period of administration is at least about 4 weeks. In some embodiments, the time period of administration is at least about 24 weeks. In some embodiments, the time period of administration is at least about one year. In some embodiments, the time period of administration is at least 4 weeks. In some embodiments, the time period of administration is at least 24 weeks. In some embodiments, the time period of administration is at least one year. In some embodiments, the time period of administration is less than about 1 day. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6 or 7 days, or within a range of any of the preceding values. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 weeks, or within a range of any of the preceding values. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, or within a range of any of the preceding values. It is understood that comparative measurements occur preferably during the morning.

**[0251]** In some embodiments, the subject is a pediatric subject. In some embodiments, the pediatric subject is less than or equal to six years old. In some embodiments, the pediatric subject is greater than six years old and less than eleven years old. In some embodiments, the pediatric subject is greater than ten years old and less than fifteen years old. In some embodiments, the pediatric subject is greater than fourteen years old and less than nineteen years old.

**[0252]** In some embodiments, the subject is an adult subject. In some embodiments, the subject is over eighteen years old. In some embodiments, the subject is female. In some embodiments, the subject is male.

**[0253]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described herein. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 9. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 11. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 12. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 13. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

**[0254]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid salt described herein.

**[0255]** For the avoidance of doubt, also provided herein is the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, or corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the corresponding methods, as described herein.

**[0256]** For the avoidance of doubt, also provided herein is use of the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

**[0257]** For the avoidance of doubt, also provided herein is use of the corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

**p-Toluenesulfonic Acid Salt**

**[0258]** In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt thereof is 4-(2-chloro-4-methoxy -5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

**[0259]** In some embodiments, the 4-(2-chloro-4-methoxy -5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt is a crystalline salt. In some embodiments, the p-toluenesulfonic acid crystalline salt has Form 1.

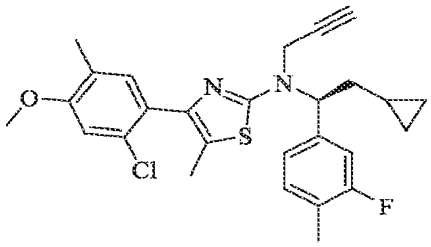
**[0260]** In some embodiments, the p-toluenesulfonic acid crystalline salt has an X-ray powder diffraction pattern as substantially shown in Figure 27. In some embodiments, the p-toluenesulfonic acid crystalline salt has a DSC thermogram substantially as depicted in Figure 28. In some embodiments, the p-toluenesulfonic acid crystalline salt has a thermogravimetric analysis (TGA) thermogram substantially as depicted in Figure 28.

**[0261]** In some embodiments, the p-toluenesulfonic acid crystalline salt has at least one X-ray powder diffraction (XRPD) peak, in terms of 2-theta (± 0.2 degrees), selected 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least two X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least three X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least four X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has characteristic X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), at 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has an endothermic peak having an onset of melt at about 156 °C (22.2 J/g) in a differential scanning calorimetry (DSC) thermogram.

**Lipidic Semi-Solid Formulation**

**[0262]** Provided herein is a lipidic semi-solid formulation, which is a pharmaceutical composition comprising:

(a) a compound of Formula (I):




(I)

or a pharmaceutically acceptable salt thereof; and
(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

**[0263]** In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or within a range of any of the preceding values.

**[0264]** In some embodiments, the pharmaceutical composition comprises an oily phase vehicle. An oily phase vehicle is a solvent that is poorly miscible with water. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 50 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 20 wt% to about 50 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 35 wt% to about 45 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 39 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 wt% of the oily phase vehicle, or within a range of any of the preceding values.

**[0265]** In some embodiments, the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the oily phase vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides are Labrafac TM Lipophile WL1349. In some embodiments, the medium-chain triglycerides are Miglyol 812N.

**[0266]** In some embodiments, the pharmaceutical composition comprises an emulsifying agent. An emulsifying agent is a compound or substance that acts as a stabilizer for emulsions. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 50 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 10 wt% to about 30 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 15 wt% to about 25 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 20 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises

about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 wt% of the emulsifying agent, or within a range of any of the preceding values.

**[0267]** In some embodiments, the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the emulsifying agent is propylene glycol dicaprylate/dicaprate. In some embodiments, the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

**[0268]** In some embodiments, the pharmaceutical composition comprises a nonionic surfactant. A nonionic surfactant is a substance with a hydrophilic head and a hydrophobic tail that has no charge that is a formulation component added to improve solubility or emulsion properties. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 50 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 10 wt% to about 30 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 15 wt% to about 25 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 19 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 wt% of the nonionic surfactant, or within a range of any of the preceding values.

**[0269]** In some embodiments, the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides. In some embodiments, the nonionic surfactant is lauroyl polyoxyl-32 glycerides. In some embodiments, the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.

**[0270]** In some embodiments, the pharmaceutical composition comprises a solubilizing agent. A solubilizing agent is a solvent that assists with solubilizing the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 50 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 20 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 15 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 11 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% of the solubilizing agent, or within a range of any of the preceding values.

**[0271]** In some embodiments, the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer. In some embodiments, the solubilizing agent is vitamin E polyethylene glycol succinate. In some embodiments, the vitamin E polyethylene glycol succinate is Kolliphor® TPGS. In some embodiments, the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.

**[0272]** In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) an oily phase vehicle;
(c) an emulsifying agent;
(d) a nonionic surfactant; and
(e) a solubilizing agent.

**[0273]** In some embodiments, the pharmaceutical composition comprises:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 35 wt% to about 45 wt% of an oily phase vehicle;
(c) about 15 wt% to about 25 wt% of an emulsifying agent;
(d) about 15 wt% to about 25 wt% of a nonionic surfactant; and
(e) about 5 wt% to about 15 wt% of a solubilizing agent.

**[0274]** In some embodiments, the pharmaceutical composition comprises:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 39 wt% of an oily phase vehicle;
(c) about 20 wt% of an emulsifying agent;

(d) about 19 wt% of a nonionic surfactant; and
(e) about 11 wt% of a solubilizing agent.

**[0275]** In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) a medium-chain triglycerides component;
(c) a propylene glycol dicaprylate/dicaprate component;
(d) a lauroyl polyoxyl-32 glycerides component; and
(e) a vitamin E polyethylene glycol succinate component.

**[0276]** In some embodiments, the pharmaceutical composition comprises:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) about 35 wt% to about 45 wt% of medium-chain triglycerides;
(c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;
(d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and
(e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.

**[0277]** In some embodiments, the pharmaceutical composition comprises:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) about 39 wt% of medium-chain triglycerides;
(c) about 20 wt% of propylene glycol dicaprylate/dicaprate;
(d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and
(e) about 11 wt% of vitamin E polyethylene glycol succinate.

**[0278]** In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 15 to about 40 centipoise at about 45 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 26 to about 30 centipoise at about 45 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 5 to about 25 centipoise at about 60 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 14 to about 18 centipoise at about 60 °C.

**[0279]** In some embodiments, the pharmaceutical composition does not comprise a combination of mannitol, croscarmellose sodium, maize starch, hydroxypropyl methylcellulose, and magnesium stearate.

**[0280]** In some embodiments, the pharmaceutical composition does not comprise at least one of mannitol, croscarmellose sodium, maize starch, hydroxypropyl methylcellulose, and magnesium stearate.

**[0281]** In some embodiments, the pharmaceutical composition comprises a compound of Formula (I), or pharmaceutically acceptable salt thereof, in crystalline form. In some embodiments, the pharmaceutical composition comprises a compound of Formula (I), or pharmaceutically acceptable salt thereof, in amorphous form. In some embodiments, the pharmaceutical composition comprises a compound of Formula (I) as a free base. In some embodiments, the crystalline form of the compound of Formula (I) is of Form I.

**[0282]** In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 75 mg to about 150 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 100 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 25 mg, based on the weight of the free base.

**[0283]** In some embodiments, the pharmaceutical composition is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film. In some embodiments, the pharmaceutical composition is in tablet form. In some embodiments, the pharmaceutical composition is in capsule form. In some embodiments, the dosage form is coated.

**[0284]** Some embodiments provide a method for preparing the pharmaceutical composition, comprising:

(a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;
(b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

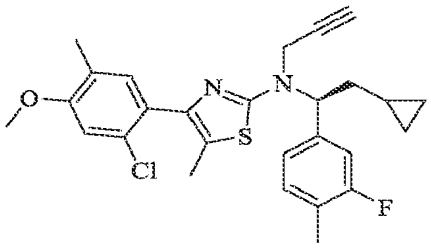
**[0285]** In some embodiments, the method further comprises:

(d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and
(e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

**Liquid Formulations**

**[0286]** Provided herein is a pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;
(b) one or more of a sweetener, an anti-oxidant, and a flavor; and
(c) a liquid vehicle.

**[0287]** In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or within a range of any of the preceding values.

**[0288]** In some embodiments, the pharmaceutical composition comprises a sweetener. A sweetener is a formulation component added to improve taste. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 1.5 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.1 w/v% to about 0.5 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.15 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.2, 0.3, 0.4, or 0.5 w/v% of the sweetener, or within a range of any of the preceding values.

**[0289]** In some embodiments, the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and avantame. In some embodiments, the sweetener is saccharin.

**[0290]** In some embodiments, the pharmaceutical composition comprises an anti-oxidant. An anti-oxidant is a formulation component included to improve stability by preventing oxidation. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.17 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.2, 0.3, 0.4, or 0.5 w/v% of the anti-oxidant, or within a range of any of the preceding values.

**[0291]** In some embodiments, the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated

hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid. In some embodiments, the anti-oxidant is butylated hydroxytoluene.

**[0292]** In some embodiments, the pharmaceutical composition comprises a flavor. A flavor is a formulation component added to mask taste through aromatics. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 0.5 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.05 w/v% to about 0.2 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.10 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19 or 0.2 w/v% of the flavor, or within a range of any of the preceding values.

**[0293]** In some embodiments, the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetrarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor. In some embodiments, the flavor is FONA orange flavor.

**[0294]** A liquid vehicle is a solvent capable of dissolving or partially dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the purposes of delivery as an oral dosing solution. In some embodiments, the pharmaceutical composition comprises about 50 w/v% to about 99.9 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 90 w/v% to about 99 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 92 w/v% to about 97 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 94.6 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 w/v% of the liquid vehicle, or within a range of any of the preceding values.

**[0295]** In some embodiments, the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the liquid vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides is Labrafac Lipophile WL1349.

**[0296]** In some embodiments, the pharmaceutical composition further comprises a surfactant. A surfactant is a formulation component added to improve solubility or emulsion properties. In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 50 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 10 w/v% to about 30 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 20 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 w/v% of the surfactant, or within a range of any of the preceding values.

**[0297]** In some embodiments, the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters. In some embodiments, the surfactant is oleoyl polyoxyl-6 glycerides. In some embodiments, the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

**[0298]** In some embodiments, the pharmaceutical composition comprises about 50 w/v% to about 90 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 70 w/v% to about 80 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 75 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 74.6 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 w/v% of the liquid vehicle, or within a range of any of the preceding values.

**[0299]** In some embodiments, the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the liquid vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides is Labrafac Lipophile WL1349.

**[0300]** In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) a sweetener;
(c) an anti-oxidant;
(d) a flavor; and
(e) a liquid vehicle.

**[0301]** In some embodiments, the pharmaceutical composition further comprises a surfactant.

**[0302]** In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
(d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and
(e) about 92 w/v% to about 97 w/v% of a liquid vehicle.

**[0303]** In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of a sweetener;
(c) about 0.17 w/v% of an anti-oxidant;
(d) about 0.1 w/v% of a flavor; and
(e) about 94.6 w/v% of a liquid vehicle.

**[0304]** In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
(d) about 0.05 w/v% to about 0.2 w/v% of a flavor;
(e) about 15 w/v% to about 25 w/v% of a surfactant; and
(f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

**[0305]** In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of a sweetener;
(c) about 0.17 w/v% of an anti-oxidant;
(d) about 0.1 w/v% of a flavor;
(e) about 20 w/v% of a surfactant; and
(f) about 75 w/v% of a liquid vehicle.

**[0306]** In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) saccharin;
(c) butylated hydroxytoluene;
(d) FONA orange flavor; and
(e) medium-chain triglycerides.

**[0307]** In some embodiments, the pharmaceutical composition further comprises oleoyl polyoxyl-6 glycerides.

**[0308]** In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and

(e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

**[0309]** In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of saccharin;
(c) about 0.17 w/v% of butylated hydroxytoluene;
(d) about 0.1 w/v% of FONA orange flavor; and
(e) about 94.6 w/v% of medium-chain triglycerides.

**[0310]** In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;
(e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and
(f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

**[0311]** In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of saccharin;
(c) about 0.17 w/v% of butylated hydroxytoluene;
(d) about 0.1 w/v% of FONA orange flavor;
(e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and
(f) about 75 w/v% of medium-chain triglycerides.

**[0312]** In some embodiments, the pharmaceutical composition comprises the compound of Formula (I) as a free base.

**[0313]** In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 50 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 100 mg/mL, based on the weight of the free base.

**[0314]** In some embodiments, the liquid pharmaceutical composition has a viscosity between about 1 to about 50 centipoise at about 25 °C.

**[0315]** Some embodiments provide a method for preparing a pharmaceutical composition comprising:

(a) mixing a liquid vehicle with a sweetener;
(b) mixing the mixture of step (a) with an anti-oxidant and a flavor;
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and
(d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

**[0316]** In some embodiments, step (a) of the method comprises mixing a liquid vehicle with a sweetener and a surfactant.

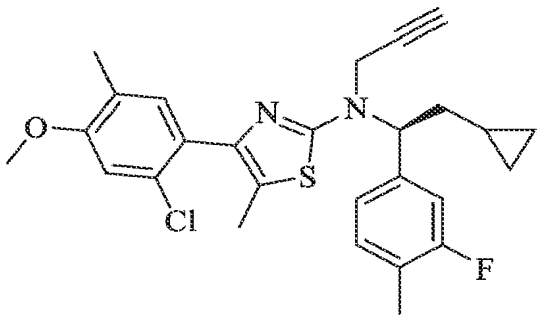
**Spray-dried dispersions**

**[0317]** The methods and uses of the present disclosure may comprise administering a spray-dried dispersion (SDDs) of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-

ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and to the use of the SDDs in the treatment of congenital adrenal hyperplasia (CAH).

**[0318]** In some embodiments, concentration and bioavailability enhancement in an aqueous environment of a low-solubility drug in a spray-dried dispersion is achieved if the SDD exhibits one or more properties, including, for example: (1) the solid dispersion is substantially homogeneous; (2) the drug is substantially amorphous; (3) the SDD has a relatively high drug loading; and (4) the SDD has a low residual solvent content. In some embodiments, the dispersion, when administered to an aqueous environment, provides at least a temporary dissolved drug concentration in the aqueous environment that is greater than the solubility of the crystalline form of the drug in the same environment. The aqueous environment can be, for example, an *in vitro* environment, such as a dissolution test media (e.g., phosphate buffered saline (PBS) solution), or an *in vivo* environment, such as the gastrointestinal (GI) tract of an animal, for example, a human. In some embodiments, the aqueous environment is the lower GI tract, such as the small intestine and large intestine.

**[0319]** Provided in the present disclosure is a spray-dried dispersion that contains a polymer and a compound having the structure of Formula (I):




(I)

or a pharmaceutically acceptable salt thereof. In some embodiments, the SDD includes a polymer selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from about 1:1 to about 1:9.

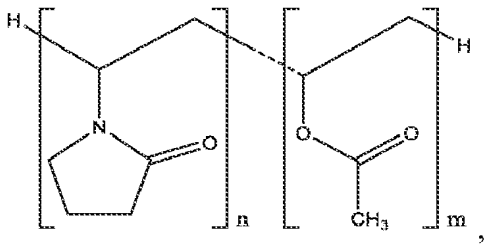
**[0320]** In some embodiments, the polymer is a neutral polymer. For example, the polymer does not contain any charged functional groups. In some embodiments, the neutral polymer is a cellulosic polymer. For example, the cellulosic polymer can be a polymer with at least one ester- and/or ether-linked substituent in which the polymer has a degree of substitution of at least 0.05 for each substituent. Examples of suitable neutral polymers include, but are not limited to, hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

**[0321]** In some embodiments, the polymer is an enteric polymer. An "enteric polymer," as used herein, is a polymeric substance that is substantially insoluble and/or substantially stable under acidic conditions exhibiting a pH of less than about 7 and which is substantially soluble or can decompose under conditions exhibiting a pH of about 7 or more. Examples of suitable enteric polymers include, but are not limited to, carboxymethyl ethyl cellulose (CMEC), cellulose acetate phthalate (CAP), cellulose acetate succinate (CAS), methylcellulose phthalate, hydroxymethyl ethyl cellulose phthalate, hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate succinate (HP-MCAS), polyvinyl alcohol phthalate, polyvinyl butyrate phthalate, polyvinyl acetal phthalate, a copolymer of vinyl acetate/maleic anhydride, a copolymer of vinylbutylether/maleic anhydride, a copolymer of styrene/maleic acid monoester, a copolymer of methyl acrylate/methacrylic acid, a copolymer of styrene/acrylic acid, a copolymer of methyl acrylate/methacrylic acid/octyl acrylate, a copolymer of methacrylic acid/methyl methacrylate, an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, a methacrylic copolymer, and mixtures thereof. In some embodiments, the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer. In some embodiments, the enteric polymer is a Eudragit® polymer sold by Evonik Industries (Essen, Germany). In some embodiments, the enteric polymer is an amino methacrylate copolymer. In some embodiments, the amino methacrylate copolymer is Eudragit® E PO/100. In some embodiments, the enteric polymer is an ammonioalkyl methacrylate copolymer. In some embodiments, the ammonioalkyl methacrylate copolymer is Eudragit® RLPO. In some embodiments, the enteric polymer is a methacrylic copolymer. In some embodiments, the methacrylic copolymer is Eudragit® L100 or Eudragit® S100.

**[0322]** In some embodiments, the polymer is a pyrrolidone polymer. For example, the pyrrolidone polymer can be a vinyl pyrrolidone polymer, such as polyvinyl pyrrolidone (PVP) or polyvinyl pyrrolidone vinyl acetate (PVP/VA), including

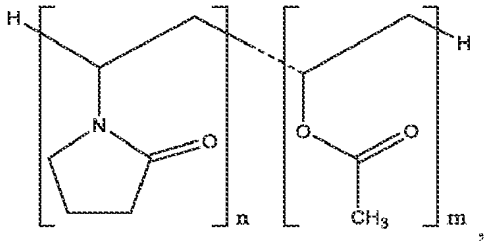
homopolymers and copolymers of PVP and homopolymers and copolymers of N-vinyl pyrrolidone. In some embodiments, the pyrrolidone polymer is PVP/VA. In some embodiments, the PVP/VA is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 30:70 to about 70:30 by weight, such as about 40:60 to about 60:40 by weight, or about 45:55 to about 55:45 by weight. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 30:70, about 35:65, about 40:60, about 45:55, about 50:50, about 55:45, about 60:40, about 65:35, or about 70:30 by weight. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight.

**[0323]** In some embodiments, the pyrrolidone polymer has the structure:



where the value of n is about 1 to about 2 times the value of m. For example, the value of n can be about 1, about 1.05, about 1.1, about 1.15, about 1.16, about 1.2, about 1.25, about 1.3, about 1.35, about 1.4, about 1.45, about 1.5, about 1.55, about 1.6, about 1.65, about 1.7, about 1.75, about 1.8, about 1.85, about 1.9, about 1.95, or about 2 times the value of m, or a value within a range defined by any of the preceding values. In some embodiments, the value of n is about 1.16 times the value of m. In some embodiments, the copolymer is copovidone, and the value of n is about 1.16 times the value of m.

**[0324]** In some embodiments, the pyrrolidone polymer has the structure:



where the value of n is 1 to 2 times the value of m. For example, the value of n can be 1, 1.05, 1.1, 1.15, 1.16, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, or 2 times the value of m, or a value within a range defined by any of the preceding values. In some embodiments, the value of n is 1.16 times the value of m. In some embodiments, the copolymer is copovidone, and the value of n is 1.16 times the value of m.

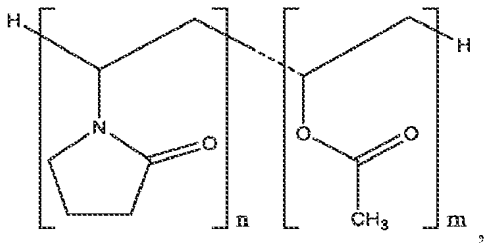
**[0325]** In some embodiments, the polymer used in the disclosed SDDs is present in an amount sufficient to increase the maximum drug concentration of the amorphous form of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the environment of use (e.g., aqueous environment) relative to a control composition that contains an equivalent amount of a crystalline form of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, but without polymer. In some embodiments, once the SDD is introduced into an environment of use (e.g., aqueous environment), the polymer increases the aqueous concentration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, relative to the control composition. It is to be understood that the control composition is free from solubilizers or other components that would materially affect the solubility of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is in solid form in the control composition.

**[0326]** In some embodiments of the SDDs, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from about 1:1 to about 1:9. For example, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer can be about 1:1 to about 1:8, about 1:1 to about 1:7, about 1:1 to about 1:6, about 1:1 to about 1:5, about 1:1 to about 1:4, about 1:1 to about 1:3, about 1:1 to about 1:2, about 1:1 to about 1:1.5, about 1:1.5 to about 1:9, or about 1:2.5 to about 1:4. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:9, about 1:8, about 1:7.5, about 1:7, about 1:6, about 1:5, about 1:4, about 1:3, about 1:2.5, about 1:2, about 1:1.5, or about

1:1, or a weight ratio within a range defined by any of the preceding values. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:9. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:1.5. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:1.

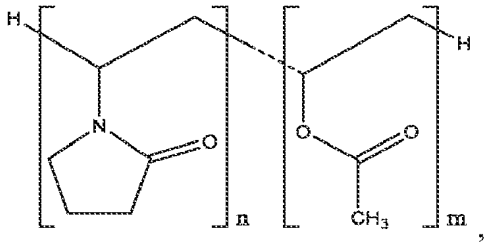
**[0327]** In some embodiments of the SDDs, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from 1:1 to 1:9. For example, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer can be 1:1 to 1:8, 1:1 to 1:7, 1:1 to 1:6, 1:1 to 1:5, 1:1 to 1:4, 1:1 to 1:3, 1:1 to 1:2, 1:1 to 1:1.5, 1:1.5 to 1:9, or 1:2.5 to 1:4. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:9, 1:8,1:7.5,1:7,1:6,1:5,1:4,1:3,1:2.5, 1:2, 1:1.5, or 1:1, or a weight ratio within a range defined by any of the preceding values. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:9. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:1.5. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:1.

**[0328]** In some embodiments, the spray dried dispersion includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



where the value of n is about 1 to about 2 times the value of m and the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight, and the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the copolymer is from about 1:1 to about 1:9.

**[0329]** In some embodiments, the spray dried dispersion includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



where the value of n is 1 to 2 times the value of m and the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of 60:40 by weight, and the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the copolymer is from 1:1 to 1:9.

**[0330]** In some embodiments of the SDDs, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer together form homogeneous particles. In some embodiments, the particles are a substantially homogeneous composition that includes the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer. As used herein, "substantially homogeneous" means that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dispersed as homogeneously as possible throughout the polymer and can be thought of as a solid solution of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, dispersed in the polymer. While the dispersion can have some concentrated domains of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the dispersion itself has a single glass transition temperature ($T_g$) which demonstrates that the dispersion is substantially homogeneous. This contrasts with a simple physical mixture of pure amorphous particles of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and pure amorphous polymer particles, which generally displays two distinct $T_g$S, one of the compound of Formula (I), or a pharmaceutically acceptable salt

thereof, and one of the polymer. "$T_g$," as used herein, is the characteristic temperature where a glassy material, upon gradual heating, undergoes a relatively rapid (e.g., 10 to 100 seconds) physical change from a glass state to a rubber state.

**[0331]** In some embodiments, the particles have a particle size distribution (D-value, $D_{50}$), of about 5 μm to about 100 μm, such as about 5 μm to about 95 μm, about 5 μm to about 90 μm, about 5 μm to about 85 μm, about 5 μm to about 80 μm, about 5 μm to about 75 μm, about 5 μm to about 70 μm, about 5 μm to about 65 μm, about 5 μm to about 60 μm, about 5 μm to about 55 μm, about 5 μm to about 50 μm, about 5 μm to about 45 μm, about 5 μm to about 40 μm, about 5 μm to about 35 μm, about 5 μm to about 30 μm, about 5 μm to about 25 μm, about 5 μm to about 20 μm, about 5 μm to about 15 μm, about 5 μm to about 10 μm, about 10 μm to about 100 μm, about 10 μm to about 95 μm, about 10 μm to about 90 μm, about 10 μm to about 85 μm, about 10 μm to about 80 μm, about 10 μm to about 75 μm, about 10 μm to about 70 μm, about 10 μm to about 65 μm, about 10 μm to about 60 μm, about 10 μm to about 55 μm, about 10 μm to about 50 μm, about 10 μm to about 45 μm, about 10 μm to about 40 μm, about 10 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about 75 μm, about 75 μm to about 100 μm, about 75 μm to about 95 μm, about 75 μm to about 90 μm, about 75 μm to about 85 μm, about 75 μm to about 80 μm, about 80 μm to about 100 μm, about 80 μm to about 95 μm, about 80 μm to about 90 μm, about 80 μm to about 85 μm, about 85 μm to about 100 μm, about 85 μm to about 95 μm, about 85 μm to about 90 μm, about 90 μm to about 100 μm, about 90 μm to about 95 μm, or about 95 μm to about 100 μm. In some embodiments, the $D_{50}$ is about 5 μm, about 10 μm, about 15 μm, about 16 μm, about 20 μm, about 25 μm, about 30 μm, about 35 μm, about 40 μm, about 45 μm, about 50 μm, about 55 μm, about 60 μm, about 65 μm, about 70 μm, about 75 μm, about 80 μm, about 85 μm, about 90 μm, about 95 μm, or about 100 μm. In some embodiments, the $D_{50}$ is about 10 μm, about 11 μm, about 12 μm, about 13 μm, about 14 μm, about 15 μm, about 16 μm, about 17 μm, about 18 μm, about 19 μm, or about 20 μm, or a value within a range defined by any of the preceding values. In some embodiments, the Dso value is about 16 μm. The Dso value can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, laser diffraction and

disc centrifugation.

**[0332]** In some embodiments, the particles have a particle size distribution (D-value, $D_{50}$), of 5 μm to 100 μm, such as 5 μm to 95 μm, 5 μm to 90 μm, 5 μm to 85 μm, 5 μm to 80 μm, 5 μm to 75 μm, 5 μm to 70 μm, 5 μm to 65 μm, 5 μm to 60 μm, 5 μm to 55 μm, 5 μm to 50 μm, 5 μm to 45 μm, 5 μm to 40 μm, 5 μm to 35 μm, 5 μm to 30 μm, 5 μm to 25 μm, 5 μm to 20 μm, 5 μm to 15 μm, 5 μm to 10 μm, 10 μm to 100 μm, 10 μm to 95 μm, 10 μm to 90 μm, 10 μm to 85 μm, 10 μm to 80 μm, 10 μm to 75 μm, 10 μm to 70 μm, 10 μm to 65 μm, 10 μm to 60 μm, 10 μm to 55 μm, 10 μm to 50 μm, 10 μm to 45 μm, 10 μm to 40 μm, 10 μm to 35 μm, 10 μm to 30 μm, 10 μm to 25 μm, 10 μm to 20 μm, 10 μm to 15 μm, 15 μm to 100 μm, 15 μm to 95 μm, 15 μm to 90 μm, 15 μm to 85 μm, 15 μm to 80 μm, 15 μm to 75 μm, 15 μm to 70 μm, 15 μm to 65 μm, 15 μm to 60 μm, 15 μm to 55 μm, 15 μm to 50 μm, 15 μm to 45 μm, 15 μm to 40 μm, 15 μm to 35 μm, 15 μm to 30 μm, 15 μm to 25 μm, 15 μm to 20 μm, 20 μm to 100 μm, 20 μm to 95 μm, 20 μm to 90 μm, 20 μm to 85 μm, 20 μm to 80 μm, 20 μm to 75 μm, 20 μm to 70 μm, 20 μm to 65 μm, 20 μm to 60 μm, 20 μm to 55 μm, 20 μm to 50 μm, 20 μm to 45 μm, 20 μm to 40 μm, 20 μm to 35 μm, 20 μm to 30 μm, 20 μm to 25 μm, 25 μm to 100 μm, 25 μm to 95 μm, 25 μm to 90 μm, 25 μm to 85 μm, 25 μm to 80 μm, 25 μm to 75 μm, 25 μm to 70 μm, 25 μm to 65 μm, 25 μm to 60 μm, 25 μm to 55 μm, 25 μm to 50 μm, 25 μm to 45 μm, 25 μm to 40 μm, 25 μm to 35 μm, 25 μm to 30 μm, 30 μm to 100 μm, 30 μm to 95 μm, 30 μm to 90 μm, 30 μm to 85 μm, 30 μm to 80 μm, 30 μm to 75 μm, 30 μm to 70 μm, 30 μm to 65 μm, 30 μm to 60 μm, 30 μm to 55 μm, 30 μm to 50 μm, 30 μm to 45 μm, 30 μm to 40 μm, 30 μm to 35 μm, 35 μm to 100 μm, 35 μm to 95 μm, 35 μm to 90 μm, 35 μm to 85 μm, 35 μm to 80 μm, 35 μm to 75 μm, 35 μm to 70 μm, 35 μm to 65 μm, 35 μm to 60 μm, 35 μm to 55 μm, 35 μm to 50 μm, 35 μm to 45 μm, 35 μm to 40 μm, 40 μm to 100 μm, 40 μm to 95 μm, 40 μm to 90 μm, 40 μm to 85 μm, 40 μm to 80 μm, 40 μm to 75 μm, 40 μm to 70 μm, 40 μm to 65 μm, 40 μm to 60 μm, 40 μm to 55 μm, 40 μm to 50 μm, 40 μm to 45 μm, 45 μm to 100 μm, 45 μm to 95 μm, 45 μm to 90 μm, 45 μm to 85 μm, 45 μm to 80 μm, 45 μm to 75 μm, 45 μm to 70 μm, 45 μm to 65 μm, 45 μm to 60 μm, 45 μm to 55 μm, 45 μm to 50 μm, 50 μm to 100 μm, 50 μm to 95 μm, 50 μm to 90 μm, 50 μm to 85 μm, 50 μm to 80 μm, 50 μm to 75 μm, 50 μm to 70 μm, 50 μm to 65 μm, 50 μm to 60 μm, 50 μm to 55 μm, 55 μm to 100 μm, 55 μm to 95 μm, 55 μm to 90 μm, 55 μm to 85 μm, 55 μm to 80 μm, 55 μm to 75 μm, 55 μm to 70 μm, 55 μm to 65 μm, 55 μm to 60 μm, 60 μm to 100 μm, 60 μm to 95 μm, 60 μm to 90 μm, 60 μm to 85 μm, 60 μm to 80 μm, 60 μm to 75 μm, 60 μm to 70 μm, 60 μm to 65 μm, 65 μm to 100 μm, 65 μm to 95 μm, 65 μm to 90 μm, 65 μm to 85 μm, 65 μm to 80 μm, 65 μm to 75 μm, 65 μm to 70 μm, 70 μm to 100 μm, 70 μm to 95 μm, 70 μm to 90 μm, 70 μm to 85 μm, 70 μm to 80 μm, 70 μm to 75 μm, 75 μm to 100 μm, 75 μm to 95 μm, 75 μm to 90 μm, 75 μm to 85 μm, 75 μm to 80 μm, 80 μm to 100 μm, 80 μm to 95 μm, 80 μm to 90 μm, 80 μm to 85 μm, 85 μm to 100 μm, 85 μm to 95 μm, 85 μm to 90 μm, 90 μm to 100 μm, 90 μm to 95 μm, or 95 μm to 100 μm. In some embodiments, the $D_{50}$ is 5 μm, 10 μm, 15 μm, 16 μm, 20 μm, 25 μm, 30 μm, 35 μm, 40 μm, 45 μm, 50 μm, 55 μm, 60 μm, 65 μm, 70 μm, 75 μm, 80 μm, 85 μm, 90 μm, 95 μm, or 100 μm. In some embodiments, the Dso is 10 μm, 11 μm, 12 μm, 13 μm, 14 μm, 15 μm, 16 μm, 17 μm, 18 μm, 19 μm, or 20 μm, or a value within a range defined by any of the preceding values. In some embodiments, the $D_{50}$ value is 16 μm. The Dso value can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, laser diffraction and disc centrifugation.

**[0333]** The SDDs of the present disclosure have a low residual solvent content. "Residual solvent content," as used herein, refers to the amount of solvent present in the SDD following spray drying, immediately upon exit from the spray dryer. The presence of solvent in the SDD lowers the glass transition temperature ($T_g$) of the dispersion. In some embodiments, mobility of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the SDD and its propensity to phase separate and crystallize decreases as the amount of residual solvent in the SDD decreases. In some embodiments, the SDDs have a residual solvent content of not more than about 10 wt%, such as not more than about 5 wt%, or not more than about 1 wt%. For example, the SDDs have a residual solvent content of about 2 wt%, about 1.9 wt%, about 1.8 wt%, about 1.7 wt%, about 1.6 wt%, about 1.5 wt%, about 1.4 wt%, about 1.3 wt%, about 1.2 wt%, about 1.1 wt%, about 1 wt%, about 0.9 wt%, about 0.8 wt%, about 0.7 wt%, about 0.6 wt%, about 0.5 wt%, or less. In some embodiments, the SDDs have a residual solvent content of less than about 2 wt%. In some embodiments, the SDDs have a residual solvent content of less than about 1 wt%. In some embodiments, the SDDs have a residual solvent content of about 0.5 wt% or less. In some embodiments, the SDDs have a residual solvent content of not more than 10 wt%, such as not more than 5 wt%, or not more than 1 wt%. For example, the SDDs may have a residual solvent content of 2 wt%, 1.9 wt%, 1.8 wt%, 1.7 wt%, 1.6 wt%, 1.5 wt%, 1.4 wt%, 1.3 wt%, 1.2 wt%, 1.1 wt%, 1 wt%, 0.9 wt%, 0.8 wt%, 0.7 wt%, 0.6 wt%, 0.5 wt%, or less. In some embodiments, the SDDs have a residual solvent content of less than 2 wt%. In some embodiments, the SDDs have a residual solvent content of less than 1 wt%. In some embodiments, the SDDs have a residual solvent content of 0.5 wt% or less.

**[0334]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the spray-dried dispersion is substantially amorphous. As used herein, "substantially amorphous" means that the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in amorphous form is at least 60 wt% and that the amount of crystalline form present does not exceed 20 wt%. In some embodiments, the compound of Formula (I),

or a pharmaceutically acceptable salt thereof, in the dispersion is "almost completely amorphous," meaning that at least 90 wt% of the drug is amorphous, or that the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the crystalline form does not exceed 10 wt%. Amounts of crystalline drug can be measured by powder X-ray diffraction (PXRD), scanning electron microscope (SEM) analysis, differential scanning calorimetry (DSC), polarized light microscopy (PLM), or any other standard quantitative or qualitative measurement used to detect crystalline material. Without wishing to be bound by any theory, it is believed that the amorphous, or non-crystalline form, in combination with the polymer, leads to greater ease of dissolution and absorption in the desired location, for example, the intestines, resulting in enhanced bioavailability as compared to a crystalline form of the compound of Formula (I) without polymer.

**Process for preparing spray-dried dispersions**

**[0335]** Provided in the present disclosure are methods for preparing a spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof, such as the SDDs described herein. In some embodiments, the method includes dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer. In some embodiments, the product obtained by spray-drying is dried to remove the solvent or solvent mixture. In some embodiments, the organic solvent is acetone.

**[0336]** The SDDs disclosed herein can be obtained by spray-drying a mixture comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, one or more polymer(s), and an appropriate solvent or solvent mixture. Spray-drying involves atomization of a liquid mixture containing, for example, a solid and a solvent or solvent mixture, and removal of the solvent or solvent mixture. Atomization can be done, for example, through a two-fluid or pressure or electrosonic nozzle, or on a rotating disk.

**[0337]** Spray-drying converts a liquid feed to a dried particulate form. In some embodiments, spray-drying involves the atomization of a liquid feed solution into a spray of droplets and contacting the droplets with hot air or gas in a drying chamber. The composition to be spray-dried can be any solution, coarse suspension, slurry, colloidal dispersion, or paste that can be atomized using the selected spray-drying apparatus. In some embodiments, the composition is a solution that is clear and free of undissolved solids. In some embodiments, the sprays are produced by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. Commercially available types of apparatus can be used to conduct the spray-drying. For example, commercial spray dryers are manufactured by Buchi Ltd. and Niro (e.g., the PSD line of spray driers manufactured by Niro). Techniques and methods for spray-drying can also be found in Perry's Chemical Engineering Handbook, 6th Ed., R. H. Perry, D. W. Green & J. O. Maloney, eds., McGraw-Hill Book Co. (1984); and Marshall, "Atomization and Spray-Drying" 50, Chem. Eng. Prog. Monogr. Series 2 (1954).

**[0338]** In some embodiments, the spray-drying is conducted with an inlet temperature of from about 40°C to about 100°C, for example, from about 60°C to about 80°C, or from about 70°C to about 75°C. In some embodiments, the spray-drying is conducted with an inlet temperature of about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 70°C, about 72°C, about 75°C, about 80°C, about 85°C, about 90°C, about 95°C, or about 100°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is about 60°C to about 80°C. In some embodiments, the spray-drying is conducted with an inlet temperature of about 61°C, about 63°C, about 65°C, about 67°C, about 69°C, about 71°C, about 73°C, about 75°C, about 77°C, about 79°C, about 81°C, about 83°C, or about 85°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is about 72°C.

**[0339]** In some embodiments, the spray-drying is conducted with an inlet temperature of from 40°C to 100°C, for example, from 60°C to 80°C, or from 70°C to 75°C. In some embodiments, the spray-drying is conducted with an inlet temperature of 40°C, 45°C, 50°C, 55°C, 60°C, 70°C, 72°C, 75°C, 80°C, 85°C, 90°C, 95°C, or 100°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is 60°C to 80°C. In some embodiments, the spray-drying is conducted with an inlet temperature of 61°C, 63°C, 65°C, 67°C, 69°C, 71°C, 73°C, 75°C, 77°C, 79°C, 81°C, 83°C, or 85°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is 72°C.

**[0340]** In some embodiments, the spray-drying is conducted with an outlet temperature of from about 20°C to about 75°C, for example, from about 25°C to about 50°C, or from about 30°C to about 40°C. In some embodiments, the spray-drying is conducted with an outlet temperature of about 20°C, about 25°C, about 30°C, about 35°C, about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 65°C, about 70°C, or about 75°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is about 25°C to about 45°C. In some embodiments, the spray-drying is conducted with an outlet temperature of about 24°C, about 26°C, about 28°C, about 30°C, about 32°C, about 34°C, about 36°C, about 38°C, about 40°C, about 42°C, about 44°C, or about 46°C, or within a range

defined by any of the preceding values. In some embodiments, the outlet temperature is about 35°C.

**[0341]** In some embodiments, the spray-drying is conducted with an outlet temperature of from 20°C to 75°C, for example, from 25°C to 50°C, or from 30°C to 40°C. In some embodiments, the spray-drying is conducted with an outlet temperature of 20°C, 25°C, 30°C, 35°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, or 75°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is 25°C to 45°C. In some embodiments, the spray-drying is conducted with an outlet temperature of 24°C, 26°C, 28°C, 30°C, 32°C, 34°C, 36°C, 38°C, 40°C, 42°C, 44°C, or 46°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is 35°C.

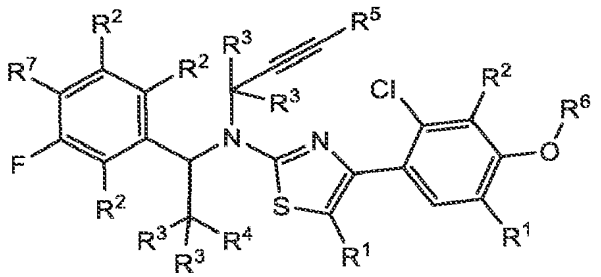
**[0342]** In some embodiments, the method involves removing the organic solvent after formation of the spray-dried dispersion. In some embodiments, the organic solvent is removed by drying the SDD. In some embodiments, a secondary drying process, such as fluidized bed drying, vacuum drying, tray drying, microwave drying, rotary drum drying or biconical vacuum drying is used to remove or reduce residual solvents, such as the organic solvent, to pharmaceutically acceptable levels. In some embodiments, the SDD is dried with a convection tray dryer.

**[0343]** In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of less than about 0.2 g/mL, or less than about 0.15 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of about 0.19 g/mL, about 0.18 g/mL, about 0.17 g/mL, about 0.16 g/mL, about 0.15 g/mL, about 0.14 g/mL, about 0.13 g/mL, about 0.12 g/mL, about 0.11 g/mL, about 0.1 g/mL, about 0.09 g/mL, about 0.08 g/mL, about 0.07 g/mL, about 0.06 g/mL or about 0.05 g/mL, or within a range defined by any of the preceding values. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of less than 0.2 g/mL, or less than 0.15 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of 0.19 g/mL, 0.18 g/mL, 0.17 g/mL, 0.16 g/mL, 0.15 g/mL, 0.14 g/mL, 0.13 g/mL, 0.12 g/mL, 0.11 g/mL, 0.1 g/mL, 0.09 g/mL, 0.08 g/mL, 0.07 g/mL, 0.06 g/mL or 0.05 g/mL, or within a range defined by any of the preceding values. The term "bulk density," as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume.

**[0344]** In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of less than about 0.3 g/mL, or less than about 0.25 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of about 0.29 g/mL, about 0.28 g/mL, about 0.27 g/mL, about 0.26 g/mL, about 0.25 g/mL, about 0.24 g/mL, about 0.23 g/mL, about 0.22 g/mL, about 0.21 g/mL, about 0.2 g/mL, or about 0.19 g/mL, or within a range defined by any of the preceding values. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of less than 0.3 g/mL, or less than 0.25 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of 0.29 g/mL, 0.28 g/mL, 0.27 g/mL, 0.26 g/mL, 0.25 g/mL, 0.24 g/mL, 0.23 g/mL, 0.22 g/mL, 0.21 g/mL, 0.2 g/mL, or 0.19 g/mL, or within a range defined by any of the preceding values. The term "tap density" or "tapped density," as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

**Deuterated Compounds**

**[0345]** Also disclosed herein are compounds having the structure of the following formula (II):

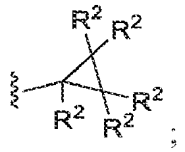


(II)

or a pharmaceutically acceptable salt thereof, wherein:

each $R^1$ is independently $C(R^A)_3$;
each $R^A$ is independently hydrogen or deuterium;
each $R^2$ is independently hydrogen or deuterium;

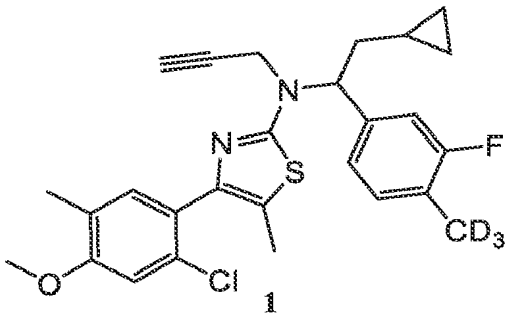
each $R^3$ is independently hydrogen or deuterium;
$R^4$ is



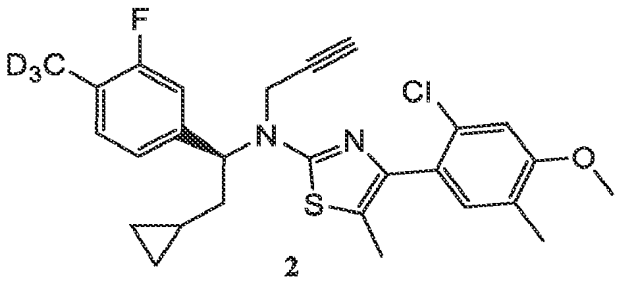
$R^5$ is hydrogen or deuterium;
$R^6$ is $C(R^A)_3$; and
$R^7$ is $C(R^B)_3$, wherein at least one of $R^A$, $R^B$, $R^2$, $R^3$ and $R^5$ is deuterium.

**[0346]** With regard to the compounds provided herein, when a particular atomic position is designated as having deuterium or "D" or "d", it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of, in certain embodiments, at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation) at each designated deuterium position.

**[0347]** In some embodiments, the compound of Formula (II) may be one of the following, or a pharmaceutically acceptable salt thereof:



1



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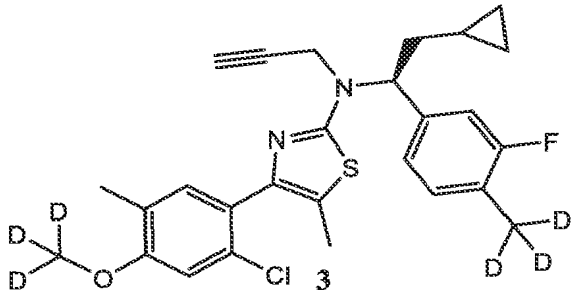

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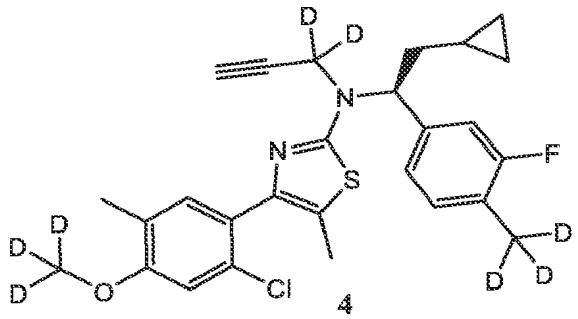
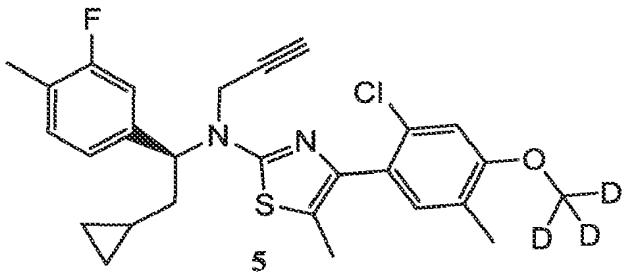


4



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**Pharmaceutical compositions**

**[0348]** The methods and uses disclosed herein can comprise administering the compound of Formula (I) as a pharmaceutical composition.

**[0349]** In some embodiments of the methods described herein, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition further comprising one or more pharmaceutically acceptable excipients.

**[0350]** Also provided herein is a pharmaceutical composition comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in any of the methods described herein.

**[0351]** In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that does not comprise a spray-dried dispersion of the compound of Formula (I), as specified, e.g., in Example 1. Accordingly, in some embodiments, the pharmaceutical composition does not comprise any of the following polymers: hydroxypropylmethylcellulose acetate succinate-L (HPMCAS-L); polyvinyl pyrrolidone vinyl acetate 64 (PVP/VA 64); HPMCAS-M; and methyl methacrylate copolymer (1:1) (Eudragit® L100).

**[0352]** In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is not the reference formulation described in Example 9. Accordingly, in some embodiments, the pharmaceutical composition does not comprise at least three of the excipients selected from caprylic/capric triglyceride (Labrafac® Lipophile, Gattefossé, France); propylene glycol dicrapolate/dicaprate (Labrafac® PG, Gattefossé, France); oleoyl polyoxyl-6 glycerides (Labrafil® M 1944 CS, Gattefossé, France); polysorbate 20; polyoxyl castor oil (Kolliphor® RH 40, BASF, Germany); polyoxyl 15 hydroxystearate (Kolliphor® HS 15, BASF, Germany); lauroyl polyoxyl-32 glycerides (Gelucire® 44/14, Gattefossé, France); d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS); and diethylene glycol monoethyl ether (Transcutol®, Gattefossé, France).

**[0353]** In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 9. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 11. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 12. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 13.

**[0354]** In some embodiments, the pharmaceutical compositions include a spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0355]** In some embodiments, the pharmaceutical composition includes the SDD comprising a compound of Formula (I) and one or more pharmaceutically acceptable excipients. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 20% to about 90% w/w of the composition, such as about 20% to about 85%,

about 20% to about 80%, about 20% to about 75%, about 20% to about 70%, about 20% to about 65%, about 20% to about 60%, about 20% to about 55%, about 20% to about 50%, about 20% to about 45%, about 20% to about 40%, about 20% to about 35%, about 20% to about 30%, about 20% to about 25%, about 25% to about 90%, about 25% to about 85%, about 25% to about 80%, about 25% to about 75%, about 25% to about 70%, about 25% to about 65%, about 25% to about 60%, about 25% to about 55%, about 25% to about 50%, about 25% to about 45%, about 25% to about 40%, about 25% to about 35%, about 25% to about 30%, about 30% to about 90%, about 30% to about 85%, about 30% to about 80%, about 30% to about 75%, about 30% to about 70%, about 30% to about 65%, about 30% to about 60%, about 30% to about 55%, about 30% to about 50%, about 30% to about 45%, about 30% to about 40%, about 30% to about 35%, about 35% to about 90%, about 35% to about 85%, about 35% to about 80%, about 35% to about 75%, about 35% to about 70%, about 35% to about 65%, about 35% to about 60%, about 35% to about 55%, about 35% to about 50%, about 35% to about 45%, about 35% to about 40%, about 40% to about 90%, about 40% to about 85%, about 40% to about 80%, about 40% to about 75%, about 40% to about 70%, about 40% to about 65%, about 40% to about 60%, about 40% to about 55%, about 40% to about 50%, about 40% to about 45%, about 45% to about 90%, about 45% to about 85%, about 45% to about 80%, about 45% to about 75%, about 45% to about 70%, about 45% to about 65%, about 45% to about 60%, about 45% to about 55%, about 45% to about 50%, about 50% to about 90%, about 50% to about 85%, about 50% to about 80%, about 50% to about 75%, about 50% to about 70%, about 50% to about 65%, about 50% to about 60%, about 50% to about 55%, about 55% to about 90%, about 55% to about 85%, about 55% to about 80%, about 55% to about 75%, about 55% to about 70%, about 55% to about 65%, about 55% to about 60%, about 60% to about 90%, about 60% to about 85%, about 60% to about 80%, about 60% to about 75%, about 60% to about 70%, about 60% to about 65%, about 65% to about 90%, about 65% to about 85%, about 65% to about 80%, about 65% to about 75%, about 65% to about 70%, about 70% to about 90%, about 70% to about 85%, about 70% to about 80%, about 70% to about 75%, about 75% to about 90%, about 75% to about 85%, about 75% to about 80%, about 80% to about 90%, about 80% to about 85%, or about 85% to about 90% w/w of the composition. In some embodiments, the SDD is present in an amount of about 40% to about 90% w/w of the composition. In some embodiments, the SDD is present in an amount of about 40% to about 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 60% to about 80% w/w of the composition. In some embodiments, the SDD is present in an amount of about 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 1% to about 20% w/w of the composition, such as about 13% w/w of the composition.

**[0356]** In some embodiments, the pharmaceutical composition includes the SDD comprising a compound of Formula (I) and one or more pharmaceutically acceptable excipients. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of 20% to 90% w/w of the composition, such as 20% to 85%, 20% to 80%, 20% to 75%, 20% to 70%, 20% to 65%, 20% to 60%, 20% to 55%, 20% to 50%, 20% to 45%, 20% to 40%, 20% to 35%, 20% to 30%, 20% to 25%, 25% to 90%, 25% to 85%, 25% to 80%, 25% to 75%, 25% to 70%, 25% to 65%, 25% to 60%, 25% to 55%, 25% to 50%, 25% to 45%, 25% to 40%, 25% to 35%, 25% to 30%, 30% to 90%, 30% to 85%, 30% to 80%, 30% to 75%, 30% to 70%, 30% to 65%, 30% to 60%, 30% to 55%, 30% to 50%, 30% to 45%, 30% to 40%, 30% to 35%, 35% to 90%, 35% to 85%, 35% to 80%, 35% to 75%, 35% to 70%, 35% to 65%, 35% to about 60%, 35% to 55%, 35% to 50%, 35% to 45%, 35% to 40%, 40% to 90%, 40% to 85%, 40% to 80%, 40% to 75%, 40% to 70%, 40% to 65%, 40% to 60%, 40% to 55%, 40% to 50%, 40% to 45%, 45% to 90%, 45% to 85%, 45% to 80%, 45% to 75%, 45% to 70%, 45% to 65%, 45% to 60%, 45% to 55%, 45% to 50%, 50% to 90%, 50% to 85%, 50% to 80%, 50% to 75%, 50% to 70%, 50% to 65%, 50% to 60%, 50% to 55%, 55% to 90%, 55% to 85%, 55% to 80%, 55% to 75%, 55% to 70%, 55% to 65%, 55% to 60%, 60% to 90%, 60% to 85%, 60% to 80%, 60% to 75%, 60% to 70%, 60% to 65%, 65% to 90%, 65% to 85%, 65% to 80%, 65% to 75%, 65% to 70%, 70% to 90%, 70% to 85%, 70% to 80%, 70% to 75%, 75% to 90%, 75% to 85%, 75% to 80%, 80% to 90%, 80% to 85%, or about 85% to 90% w/w of the composition. In some embodiments, the SDD is present in an amount of 40% to 90% w/w of the composition. In some embodiments, the SDD is present in an amount of 40% to 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of 60% to 80% w/w of the composition. In some embodiments, the SDD is present in an amount of 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 1% to about 20% w/w of the composition, such as about 13% w/w of the composition.

**[0357]** In some embodiments of the pharmaceutical compositions disclosed herein (e.g., a composition including an SDD), the pharmaceutically acceptable excipient is selected from the group consisting of a filler, a lubricant, and combinations thereof. In some embodiments, the pharmaceutical excipients are selected from the group consisting of a glidant, a filler, a disintegrant, a lubricant, and a combination thereof.

**[0358]** In some embodiments, the pharmaceutical composition includes a filler. In some embodiments, the filler is selected from among binders, diluents, disintegrants, glidants, surfactants, and combinations thereof.

**[0359]** In some embodiments, the filler include saccharides (e.g., sugars, starch, and cellulose), gelatin, calcium carbonate, and synthetic polymers (e.g., polyvinylpyrrolidone, polyethylene glycol, and poloxamers (e.g., Poloxamer 188, a copolymer of polyoxyethylene and polyoxypropylene)). Exemplary fillers include, but are not limited to, glucose,

sucrose, lactose, a starch, including modified starches such as sodium starch glycolate (e.g., Explotab®), xylitol, dextrin, saccharose, sorbitol, mannitol (e.g., Parteck® M 200 (mannitol with an average particle size of about 50 μm to about 500 μm) or Parteck® M 100 (mannitol with an average particle size of less than 212 μm)), a cellulose, a polyvinylpyrrolidone, a polyethylene glycol, a polyvinyl alcohol, a polymethacrylate, dibasic calcium phosphate, magnesium stearate, calcium stearate, sodium stearate, stearic acid, hydrogenated vegetable oils, a mineral oil, sodium lauryl sulfate, magnesium lauryl sulfate, glyceryl palmitostearate, sodium benzoate, sodium stearyl fumarate, colloidal silicon dioxide, sodium benzoate, sodium oleate, sodium acetate, aliginic acid, alginates (e.g., sodium alginate), calcium silicate, and ion exchange resins. Exemplary cellulose fillers include microcrystalline cellulose (e.g., Avicel® PH-101 (microcrystalline cellulose with an average particle size of approximately 50 μm) or Avicel® PH 200 (microcrystalline cellulose with an average particle size of approximately 180 μm)), methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethylcellulose. Exemplary fillers include cross-linked polyvinylpyrrolidone such as with an average particle size of 90 μm to 130 μm) or with an average particle size of 10 μm to 30 μm). Other fillers known to those of skill in the art are also contemplated as being useful when formulated in the pharmaceutical compositions described herein.

**[0360]** In some embodiments, the filler is a binder. Binders include agents that hold the active pharmaceutical ingredient (e.g., spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof) and inactive ingredients together in a cohesive mix. Exemplary binders include, but are not limited to, glucose, sucrose, lactose, a starch, including modified starches such as sodium starch glycolate (Explotab®), xylitol, dextrin, saccharose, sorbitol, mannitol (e.g., Parteck® M 200 (mannitol with an average particle size of about 50 μm to about 500 μm), Parteck® M 100 (mannitol with an average particle size of less than 212 μm)), gelatin, gum tragacanth, acacia mucilage, a cellulose, a polyvinylpyrrolidone, a polyethylene glycol, a polyvinyl alcohol, a polymethacrylate, and sodium starch glycolate. Exemplary cellulose fillers include microcrystalline cellulose (e.g., Avicel® PH-101 (microcrystalline cellulose with an average particle size of approximately 50 μm) or Avicel® PH 200 (microcrystalline cellulose with an average particle size of approximately 180 μm)), cellulose ethers, methyl cellulose, ethyl cellulose, croscarmellose sodium, sodium carboxy methyl cellulose starches, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose. Exemplary polyvinylpyrrolidone fillers include cross-linked polyvinylpyrrolidone such as Kollidon® CL (crospovidone with an average particle size of 90 μm to 130 μm) or Kollidon® CL-SF (crospovidone with an average particle size of 10 μm to 30 μm). Other binders known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

**[0361]** In some embodiments, the filler is a diluent. Suitable diluents include, but are not limited to, lactose, mannitol, isomalt, sucrose, dextrose, and sorbitol.

**[0362]** In some embodiments, the filler is a disintegrant. Disintegrants include any agent that promotes breakup of the formulation in an aqueous environment, for example, to promote more rapid release of the active pharmaceutical ingredient (e.g., the compound of Formula (I), or a pharmaceutically acceptable salt thereof). Exemplary disintegrants include, but are not limited to, starch and modified starches, such as corn starch, potato starch, sodium starch glycolate or croscarmellose sodium, alginic acid, alginates, such as sodium alginate, polyvinylpyrrolidone, bentonite, methylcellulose, agar, carboxymethylcellulose, crospovidone, acid-carbonate effervescent systems, such as citric acid with bicarbonate salts, and ion exchange resins. Other disintegrants known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

**[0363]** In some embodiments, the pharmaceutical composition comprises a disintegrant. In some embodiments, the pharmaceutical composition comprises about 1 w/w% to about 30 w/w% of the disintegrant. In some embodiments, the pharmaceutical composition comprises about 5 w/w% to about 15 w/w% of the disintegrant. In some embodiments, the pharmaceutical composition comprises about 10 w/w% of the disintegrant. In some embodiments, the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, and sodium bicarbonate. In some embodiments, the disintegrant is croscarmellose sodium.

**[0364]** In some embodiments, the filler is a glidant. Glidants can be used to improve the flowability of a powder or granules or both. Glidants include, but are not limited to, silicone dioxide, such as colloidal silicon dioxide or hydrated silicon dioxide, magnesium silicate, magnesium aluminometasilicate, talc, starch, calcium silicate, light anhydrous silicic acid, and silicon dioxide aerogels.

**[0365]** In some embodiments, the pharmaceutical composition comprises a glidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 5 w/w% of the glidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 1 w/w% of the glidant. In some embodiments, the pharmaceutical composition comprises about 0.67 w/w% of the glidant. In some embodiments, the glidant is selected from calcium silicate, silicon dioxide, and talc. In some embodiments, the glidant is calcium silicate.

**[0366]** In some embodiments, the filler is a surfactant, wetting agent, solubilizer, or combination thereof. Examples include, but are not limited to, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., Tween®), polyoxyethylene stearates, sodium dodecylsulfate, tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton). Other examples

include, but are not limited to, poloxamers such as Pluronic® F68, F127, and F108, which are block copolymers of ethylene oxide and propylene oxide, and polyxamines such as Tetronic® 908 (also known as Poloxamine® 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (available from BASF), dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol® OT, which is a dioctyl ester of sodium sulfosuccinic acid (available from American Cyanimid), Duponol® P, which is a sodium lauryl sulfate (available from DuPont), Triton® X-200, which is an alkyl aryl polyether sulfonate (available from Rohm and Haas), Tween® 20 and Tween® 80, which are polyoxyethylene sorbitan fatty acid esters (available from ICI Specialty Chemicals), Carbowax™ 3550 and 934, which are polyethylene glycols (available from Union Carbide), Crodesta™ F-110, which is a mixture of sucrose stearate and sucrose distearate, and Crodesta™ SL-40 (both available from Croda Inc.), and SA90HCO, which has the chemical formula $C_{18}H_{37}$-$CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$.

**[0367]** In some embodiments, the pharmaceutical composition comprises a filler. In some embodiments, the pharmaceutical composition comprises about 30 w/w% to about 99 w/w% of the filler. In some embodiments, the pharmaceutical composition comprises about 50 w/w% to about 90 w/w% of the filler. In some embodiments, the pharmaceutical composition comprises about 75.5 w/w% of the filler. In some embodiments, the filler is selected from mannitol, microcrystalline cellulose, lactose, starch, isomalt, silicified microcrystalline cellulose, Dicalcium Phosphate, maltodextrin, and a combination thereof. In some embodiments, the filler is a combination of mannitol and microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 30 w/w% to about 80 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 50 w/w% to about 60 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 56 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 1 w/w% to about 50 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 10 w/w% to about 30 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 20 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose.

**[0368]** In some embodiments, the pharmaceutical composition includes a lubricant. Lubricants are agents added to pharmaceutical formulations to reduce friction during processing and prevent ingredients from clumping together. Exemplary lubricants include, but are not limited to, talc, starch, magnesium stearate, calcium stearate, sodium stearate, zinc stearate, stearic acid, vegetable stearin, adipic acid, waxy fatty acids, such as glyceryl behenate, a hydrogenated vegetable oil, a mineral oil, a polyethylene glycol, lycopodium, sodium lauryl sulfate, magnesium lauryl sulfate, glyceryl palmitostearate, sodium benzoate, sodium chloride, sterotex, glycerol monostearate, sodium stearyl fumarate, colloidal silicon dioxide, sodium benzoate, sodium oleate, and sodium acetate. Other lubricants known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

**[0369]** In some embodiments, the pharmaceutical composition comprises a lubricant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 10 w/w% of the lubricant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 1 w/w% of the lubricant. In some embodiments, the pharmaceutical composition comprises about 0.5 w/w% of the lubricant. In some embodiments, the pharmaceutical lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid sodium lauryl sulfate, sodium oleate, glyceryl behenate, and talc. In some embodiments, the lubricant is sodium stearyl fumarate.

**[0370]** In some embodiments, the pharmaceutical composition comprises:

(a) the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;
(b) a glidant;
(c) a filler; and
(d) a disintegrant.

**[0371]** In some embodiments, the pharmaceutical composition comprises:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;
(b) about 0.1 w/w% to about 1 w/w% of a glidant;
(c) about 50 w/w% to about 90 w/w% of a filler; and
(d) about 5 w/w% to about 0.2 w/w% of a disintegrant.

**[0372]** In some embodiments, the pharmaceutical composition comprises:

(a) about 13 w/w% of the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;

(b) about 0.67 w/w% of a glidant;
(c) about 75.5 w/w% of a filler; and
(d) about 10 w/w% of a disintegrant.

**[0373]** In some embodiments, the pharmaceutical composition comprises:

(a) the spray-dried dispersion of Example 3;
(b) calcium silicate;
(c) a combination of mannitol and microcrystalline cellulose; and
(d) croscarmellose sodium.

**[0374]** In some embodiments, the pharmaceutical composition comprises:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of Example 3;
(b) about 0.1 w/w% to about 1 w/w% of calcium silicate;
(c) about 50 w/w% to about 60 w/w% of mannitol and about 10 w/w% to about 30 w/w% of microcrystalline cellulose; and
(d) about 5 w/w% to about 0.2 w/w% of croscarmellose sodium.

**[0375]** In some embodiments, the pharmaceutical composition comprises:

(a) about 13 w/w% of the spray-dried dispersion of Example 3;
(b) about 0.67 w/w% of calcium silicate;
(c) about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose; and
(d) about 10 w/w% of croscarmellose sodium.

**[0376]** Additional excipients can be included in the pharmaceutical formulations of the present disclosure. Further examples of excipients include, but are not limited to, pigments, colorants, flavoring agents, preservatives, and sweeteners. Flavors and colors can be added to improve the taste or appearance of a formulation. Examples of preservatives used in pharmaceutical compositions are aromatic alcohols, such as benzyl or phenol alcohol, antioxidants such as vitamin A, vitamin E, vitamin C, and selenium, amino acids such as cysteine and methionine, citric acid and sodium citrate, or synthetic preservatives such as methyl paraben and propyl paraben. Sweeteners can be added to make the ingredients more palatable, especially in chewable tablets or liquids like syrups.

**[0377]** Also provided are methods for preparing a pharmaceutical composition, such as a pharmaceutical composition of the present disclosure. In some embodiments, the method includes combining the spray-dried dispersion described herein with one or more pharmaceutically acceptable excipients, e.g., a pharmaceutically acceptable excipient described herein.

**[0378]** In some embodiments, the method for preparing the pharmaceutical composition comprises:

(a) blending the spray-dried dispersion described herein, with a glidant;
(b) further blending the blend of step (a) with a filler and a disintegrant;
(c) screening the blend of step (b) to break up aggregates and assist with blend uniformity;
(d) further blending the intragranular blend of step (c);
(e) compaction of the intragranular blend of step (d) via roller compaction to form granules; and
(f) milling of ribbon from roller compaction into granules of step (e).

**[0379]** In some embodiments, the spray-dried dispersion is the spray-dried dispersion described in Example 3.

**[0380]** The pharmaceutical compositions of the present disclosure are formulated for oral administration. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media can be employed. For solid oral preparations such as, for example, powders, capsules, caplets, gelcaps, and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

**[0381]** Oral pharmaceutical dosage forms can be solid, gel, or liquid. In some embodiments, the dosage form is a solid dosage form. In some embodiments, the solid dosage form is a pill, tablet, capsule, caplet, gelcaps, granules, powder, sachet, melting strip, or melting film. In some embodiments, the solid dosage form is coated. In some embodiments, the

coating is an enteric coating, a sugar coating, or a film coating. In some embodiments, the solid dosage form is a coated particle, coated tablet, enterocoated tablet, or enterocoated capsule. In some embodiments, the solid dosage form is a pill or tablet. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric coated, sugar coated or film coated. In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a powder, solution, or suspension (e.g., in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides), or is encapsulated in a capsule (gelatin or cellulose base capsule). Capsules can be hard or soft gelatin capsules, while granules and powders can be provided in non-effervescent or effervescent form with a combination of other ingredients known to those skilled in the art.

**[0382]** The pharmaceutical compositions of the present disclosure can contain, per dosage unit, e.g., tablet, capsule, powder, and the like, an amount of the active ingredient necessary to deliver an effective dose as described above.

**[0383]** In some embodiments, the pharmaceutical compositions of the present disclosure are formulated in unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg in the unit dosage form. For example, about 5 mg to about 175 mg, about 5 mg to about 150 mg, about 5 mg to about 125 mg, about 5 mg to about 100 mg, about 5 mg to about 75 mg, about 5 mg to about 50 mg, about 5 mg to about 25 mg, about 25 mg to about 200 mg, about 25 mg to about 175 mg, about 25 mg to about 150 mg, about 25 mg to about 125 mg, about 25 mg to about 100 mg, about 25 mg to about 75 mg, about 25 mg to about 50 mg, about 50 mg to about 200 mg, about 50 mg to about 175 mg, about 50 mg to about 150 mg, about 50 mg to about 125 mg, about 50 mg to about 100 mg, about 50 mg to about 75 mg, about 75 mg to about 200 mg, about 75 mg to about 175 mg, about 75 mg to about 150 mg, about 75 mg to about 125 mg, about 75 mg to about 100 mg, about 100 mg to about 200 mg, about 100 mg to about 175 mg, about 100 mg to about 150 mg, about 100 mg to about 125 mg, about 125 mg to about 200 mg, about 125 mg to about 175 mg, about 125 mg to about 150 mg, about 150 mg to about 200 mg, about 150 mg to about 175 mg, or about 175 mg to about 200 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg to about 125 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg, about 10 mg, about 25 mg, about 35 mg, about 50 mg, about 65 mg, about 75 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, or about 200 mg in the unit dosage form, or within a range defined by any of the preceding values. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg in the unit dosage form.. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 5 mg to 250 mg in the unit dosage form. For example, 5 mg to 175 mg, 5 mg to 150 mg, 5 mg to 125 mg, 5 mg to 100 mg, 5 mg to 75 mg, 5 mg to 50 mg, 5 mg to 25 mg, 25 mg to 200 mg, 25 mg to 175 mg, 25 mg to 150 mg, 25 mg to 125 mg, 25 mg to 100 mg, 25 mg to 75 mg, 25 mg to 50 mg, 50 mg to 200 mg, 50 mg to 175 mg, 50 mg to 150 mg, 50 mg to 125 mg, 50 mg to 100 mg, 50 mg to 75 mg, 75 mg to 200 mg, 75 mg to 175 mg, 75 mg to 150 mg, 75 mg to 125 mg, 75 mg to 100 mg, 100 mg to 200 mg, 100 mg to 175 mg, 100 mg to 150 mg, 100 mg to 125 mg, 125 mg to 200 mg, 125 mg to 175 mg, 125 mg to 150 mg, 150 mg to 200 mg, 150 mg to 175 mg, or 175 mg to 200 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 25 mg to 125 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 75 mg to 150 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 5 mg, 10 mg, 25 mg, 35 mg, 50 mg, 65 mg, 75 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg in the unit dosage form, or within a range defined by any of the preceding values. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 50 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 100 mg in the unit dosage form. In some embodiments, the pharmaceutical compositions of the present disclosure are formulated as a tablet. In some embodiments, the tablet is coated. In some embodiments, the pharmaceutical compositions of the present disclosure are formulated as capsules. In some embodiments, the pharmaceutical compositions are in sachet form. In some embodiments, the pharmaceutical compositions are in granule form.

**[0384]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 25 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 75 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 100 mg, based on the weight of the

free base.

**[0385]** In some embodiments, the pharmaceutical composition is administered in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**[0386]** In some embodiments, the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**[0387]** The daily dosage of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition as described in the present disclosure can be varied over a wide range from about 1.0 mg to about 10,000 mg per adult human per day, or higher, or any range therein. For oral administration, the compositions can be provided in the form of tablets containing, for example, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2.5 mg, about 5.0 mg, about 10.0 mg, about 15.0 mg, about 25.0 mg, about 50.0 mg, about 75.0 mg, about 100 mg, about 150 mg, about 200 mg, about 250 or about 500 milligrams of the compound of Formula (I), or pharmaceutically acceptable salt thereof, for the symptomatic adjustment of the dosage to the subject to be treated. In some embodiments, an effective amount of the compound of Formula (I), or pharmaceutically acceptable salt thereof, can be supplied at a dosage level of from about 0.1 mg/kg to about 1000 mg/kg of body weight per day, or any range therein, for example, the range can be from about 0.5 mg/kg to about 500 mg/kg, about 1.0 mg/kg to about 250 mg/kg, about 0.1 mg/kg to about 100 mg/kg, about 0.1 mg/kg to about 50.0 mg/kg of body weight per day, about 0.1 mg/kg to about 15.0 mg/kg of body weight per day, about 0.5 mg/kg to about 7.5 mg/kg of body weight per day, or any amount to range therein. In some embodiments, an effective amount of the compound of Formula (I), or pharmaceutically acceptable salt thereof, can be supplied at a dosage level of from 0.1 mg/kg to 1000 mg/kg of body weight per day, or any range therein, for example, the range can be from 0.5 mg/kg to 500 mg/kg, 1.0 mg/kg to 250 mg/kg, 0.1 mg/kg to 100 mg/kg, 0.1 mg/kg to 50.0 mg/kg of body weight per day, 0.1 mg/kg to 15.0 mg/kg of body weight per day, 0.5 mg/kg to 7.5 mg/kg of body weight per day, or any amount to range therein. A pharmaceutical composition as provided herein can be administered on a regimen of 1 to 4 times per day or in a single daily dose.

**[0388]** In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 25 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 50 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 75 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 100 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 150 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 200 mg, based on the weight of the free base.

**[0389]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 25 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 75 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 100 mg, based on the weight of the free base.

**[0390]** In some embodiments, the daily dose of the pharmaceutical composition is about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 150 mg of the compound of Formula (I),

or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**[0391]** In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**[0392]** In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**[0393]** In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof, twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**[0394]** Factors associated with the particular subject being treated, including subject age, weight, diet, and time of administration, can result in the need to adjust dosages. In some embodiments, the subject is a human adult. In some embodiments, the subject is a pediatric subject.

**[0395]** One skilled in the art will recognize that both *in vivo* and *in vitro* trials using suitable, known, and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder. One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy subjects and/or those suffering from a given disorder, can be completed according to methods well known in the clinical and medical arts. For example, determining proper dosages for pediatric subjects can be determined using known methods, including weight, age, and models such as Simcyp® Pediatric Simulation modeling (CERTARA, Princeton, N.J.) which can be used to establish a pharmacokinetic approach for dosing that takes into account subject age, ontogeny of the clearance pathways that a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and body surface area (BSA).

**[0396]** In some embodiments, the pharmaceutical compositions of the present disclosure are stable for at least 3 months. In some embodiments, the pharmaceutical compositions are stable for at least 6 months. In some embodiments, the pharmaceutical compositions are stable for at least 9 months. In some embodiments, the pharmaceutical compositions are stable for at least 12 months. For example, the compositions do not exhibit a change (e.g., greater than 5%) in appearance, pH, percent impurities, activity (as measured by in vitro assays), or osmolarity over time, e.g., at least 3 months, 6 months, 9 months, or at least 12 months as compared to the original composition after manufacturing. In some embodiments, the pharmaceutical compositions do not exhibit a significant change, as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in one or more of appearance, pH, percent impurities, activity (as measured by *in vitro* assays), or osmolarity over time, e.g., at least 12 months as compared to the original pharmaceutical composition after manufacturing.

**Kits**

**[0397]** Also provided are kits. Typically, a kit includes one or more pharmaceutical compositions as described herein, e.g., a pharmaceutical composition containing, e.g., a spray-dried dispersion as described in Examples 1-4, or the formulation described in Example 9. In certain embodiments, a kit can include one or more delivery systems, e.g., for delivering or administering the pharmaceutical composition as provided herein, and directions for use of the kit (e.g., instructions for treating a subject). In some embodiments, the kit can include a pharmaceutical composition as described herein and a label that indicates that the contents are to be administered to a subject with congenital adrenal hyperplasia. The actual dose of the compound of Formula (I), or pharmaceutically acceptable salt thereof, provided herein depends on the specific formulation, the weight of the patient, and on the condition to be treated.

EXAMPLES

**Example 1: Spray-dried dispersion formulations containing the compound of Formula (I) and various polymers**

***Spray-dried** dispersion **formulations***

**[0398]** A series of spray-dried dispersion (SDD) formulations containing the compound of Formula (I) and a polymer were prepared. The SDD formulations included: (1) 10% compound of Formula (I)/90% hydroxypropylmethylcellulose acetate succinate-L (HPMCAS-L); (2) 25% compound of Formula (I)/75% HPMCAS-L; (3) 40% compound of Formula (I)/60% HPMCAS-L; (4) 25% compound of Formula (I)/75% polyvinyl pyrrolidone vinyl acetate 64 (PVP/VA 64); (5) 25% compound of Formula (I)/60% Cabosil (fumed silica)/15% HPMCAS-L; (6) 25% compound of Formula (I)/75% HPMCAS-M; and (7) 25% compound of Formula (I)/75% methyl methacrylate copolymer (1:1) (Eudragit® L100).

**[0399]** The PVP/VA polymer was a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate with a ratio of 60:40 by weight 1-vinyl-2-pyrrolidone:vinyl acetate with an average molecular weight of 45,000-70,000 (copovidone, sold as Kollidon® VA 64, BASF, Florham Park, NJ). The HPMCAS was a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose that was either grade L (HPMCAS-L), with an acetyl content of 5-9%, a succinoyl content of 14-18%, a methoxyl content of 20-24%, and a hydroxypropoxy content of 5-9% (sold by Shin-Etsu, Japan); or grade M (HPMCAS-M), with an acetyl content of 7-11%, a succinoyl content of 10-14%, a methoxyl content of 21-25%, and a hydroxypropoxy content of 5-9% (sold by Shin-Etsu, Japan).

***Dissolution performance***

**[0400]** Dissolution performance of several of the SDD formulations described above was tested (see FIG. 1). 1000 μgA/mL of each SDD was tested in 0.5 wt% simulated intestinal fluid (SIF) in PBS, pH 6.5. Samples were tested at 5, 10, 20, 45, 90, and 1200 minutes. A lipid formulation containing 10% of the compound of Formula (I) was used as a control. The results are shown in Table 4, below.

**Table 4. Dissolution data of various SDDs**

| Sample | $C_{max90}$ (μg/mL) | $AUC_{90}$ (min*μg/mL) | $C_{mix90}$ (μg/mL) | $Ultra_{90}$ (μg/mL) | $C_{1200}$ (μg/mL) | $Ultra_{1200}$ (μg/mL) |
|---|---|---|---|---|---|---|
| 2 | 762 | 66,080 | 743 | 210 | 671 | 166 |
| 4 | 322 | 27,330 | 306 | 109* | 268 | 199 |
| 6 | 718 | 62,240 | 708 | 202 | 632 | 217 |
| 7 | 742 | 60,600 | 742 | 113* | 674 | 194 |
| Control | 802 | 69,580 | 800 | 253 | 799 | 270 |
| *Large variability between replicates, high value discarded | | | | | | |

***Non-sink dissolution***

**[0401]** A membrane flux assay was performed (see, e.g., Stewart et al., Mol. Pharm. (2017) 14:2032-2046) and non-sink dissolution data was collected for several of the SDD formulations described above and compared to the compound

of Formula (I) and several reference formulations, including a semi-solid lipidic formulation (Reference Formulation 1) and two self-emulsifying drug delivery system (SEDDS) formulations (Reference Formulations 2 and 3). The components of the Reference Formulations are shown in Table 5, below, and include, in addition to the compound of Formula (I), caprylic/capric triglyceride (Labrafac® Lipophile, Gattefossé, France); propylene glycol dicrapolate/dicaprate (Labrafac® PG, Gattefossé, France); oleoyl polyoxyl-6 glycerides (Labrafil® M 1944 CS, Gattefossé, France); polysorbate 20; polyoxyl castor oil (Kolliphor® RH 40, BASF, Germany); polyoxyl 15 hydroxystearate (Kolliphor® HS 15, BASF, Germany); lauroyl polyoxyl-32 glycerides (Gelucire® 44/14, Gattefossé, France); d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS); and diethylene glycol monoethyl ether (Transcutol®, Gattefossé, France).

**Table 5. Reference formulations (capsules)**

| Formulation (mg/caps) | Ref. Formulation 1 | Ref. Formulation 2 | Ref. Formulation 3 |
|---|---|---|---|
| **Formula (I)** | 50.0 | 50.0 | 50.0 |
| **Labrafac® Lipophile** | 196.0 | 100.0 | 100.0 |
| **Labrafac® PG** | 102.0 | - | - |
| **Labrafil® M 1944 CS** | - | 135.0 | 46.0 |
| **Polysorbate 20** | - | - | 89.9 |
| **Kolliphor® RH 40** | - | - | 100.0 |
| **Kolliphor® HS 15** | - | 165.0 | - |
| **Gelucire® 44/14** | 95.0 | - | - |
| **TPGS** | 57.0 | - | 65.0 |
| **Transcutol®** | - | 50.0 | 50.0 |
| ***Total*** | 500.0 | 500.0 | 500.0 |

**[0402]** The assay measured the flux across simulated gastric and intestinal walls via UV spectroscopy (μDiss ProfilerTM, Pion Inc., Billerica, MA). Briefly, the assay was performed as follows. A vertical membrane flux cell consisting of a donor compartment and a receiver compartment, and separated by an Accurel PP 1E (55% porous, 100 μm thickness) polypropylene membrane (3M, Maplewood, MN) (FIG. 2), was impregnated with 50 μL of Pion GIT-0 lipid solution consisting of 20% w/w phospholipid dissolved into dodecane (Pion Inc., Billerica, MA) and attached to the receiver vessel. Both the donor and receiver compartments were agitated by magnetic stirring. The receiver compartment contained a plastic spacer and grating to elevate the stir bar above the membrane. Samples were introduced to the donor vessel by pre-weighing directly into the donor vessel and subsequently adding dissolution medium. Once the dissolution medium was added to the donor vessel, the receiver vessel was inserted into the donor vessel and suspended vertically 5 mm above the donor compartment by a plastic sleeve. For this assay, the simulated gastric (feed) media was 0.1 N HCl, pH 2 and included 200 μgA/mL of each SDD, and the simulated intestinal (receiver) media was 0.5 wt% SIF in PBS, pH 6.5 and included 100 μgA/mL of each SDD. The temperature for the assay was maintained at 44.5°C. UV probes (10 mm path length) connected to a Rainbow UV spectrometer (Pion Inc.) system were used to determine the apparent drug concentration in the receiver vessels. Samples of the donor compartment were removed with a disposable pipet for centrifugation followed by HPLC and DLS analysis of the supernatant. The results are shown in FIG. 3 and Table 6, below.

**Table 6. Non-sink dissolution data**

| Sample | $C_{maxGB}$ (μg/mL) | $C_{max90\ IB}$ (μg/mL) | $AUC_{4\text{-}90IB}$ (min*μg/mL) | $C_{90}$ (μg/mL) | $Ultra_{90}$ (μg/mL) | $C_{1200}$ (μg/ML) |
|---|---|---|---|---|---|---|
| **Formula (I)** | 0 | 1 | 10 | 0 | 0 | 3 |
| **1** | 6 | 80 | 6,800 | 80 | 79 | 90 |
| **2** | 17 | 74 | 6,240 | 73 | 73 | 86 |
| **4** | 6 | 4 | 200 | 4 | 5 | 36 |
| **5** | 23 | 55 | 3,180 | 55 | 54 | 83 |
| **6** | 35 | 71 | 6,070 | 71 | 77 | 83 |

(continued)

| Sample | $C_{maxGB}$ (μg/mL) | $C_{max90\ IB}$ (μg/mL) | $AUC_{4\text{-}90IB}$ (min*μg/mL) | $C_{90}$ (μg/mL) | $Ultra_{90}$ (μg/mL) | $C_{1200}$ (μg/ML) |
|---|---|---|---|---|---|---|
| **Ref. Formulation 1** | 205 | 109 | 9,050 | 109 | - | - |
| **Ref. Formulation 2** | 249 | 120 | 10,160 | 120 | - | - |
| **Ref. Formulation 3** | 218 | 107 | 9,100 | 107 | - | - |

**[0403]** The membrane flux of 1 mg/mL gastric barrier/intestinal barrier (GB/IB) 0.5 wt% SIF doses of the compound of Formula (I) and spray-dried dispersions (2) 25% compound of Formula (I)/75% HPMCAS-L and (4) 25% compound of Formula (I)/75% PVP/VA 64 were also determined. The results are shown in FIG. 4 as receiver concentration vs. time and flux vs. time (smoothed derivative of receiver concentration x volume/surface area).

**Example 2: Characterization of a spray-dried dispersion containing 25% of the compound of Formula (I) and 75% of a polyvinyl pyrrolidone vinyl acetate (PVP/VA) polymer**

***SDD stability screening***

**[0404]** Several of the SDDs described in Example 1 were tested for chemical and physical stability. Wet SDD stability studies were performed, with samples stored at both 5°C and 25°C. Measurements were taken after 1 week and 2 weeks of storage. The results are shown in Table 7 below. The column with a retention time of 32.36 min correlates with the compound of Formula (I).

**Table 7. Wet SDD stability data**

| **Retention time (min)** | | | 11.04 | 16.79 | 17.26 | 30.94 | 32.26 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Relative retention time** | | | 0.34 | 0.52 | 0.53 | 0.96 | 1.00 | | | |
| | **Storage temp** | **Timepoint** | | | | | | **Total impurities** | **Potency (mgA/g)** | **Std Dev** |
| **Ref. Std.** | | | | | | 0.37 | 99.63 | 0.37 | | |
| **Formula (I)** | | | | | | 0.26 | 99.74 | 0.26 | | |
| **Sample** 1 | | initial | | 0.13 | 0.16 | 0.25 | 99.46 | 0.54 | 100 | 1.3 |
| | 5°C | 1 week | | 0.03 | 0.03 | 0.26 | 99.69 | 0.31 | 99 | 0.0 |
| | | 2 weeks | | 0.12 | 0.16 | 0.28 | 99.45 | 0.55 | 99 | 0.5 |
| | 25°C | 1 week | | 0.03 | 0.04 | 0.26 | 99.67 | 0.33 | 99 | 0.3 |
| | | 2 weeks | | 0.21 | 0.27 | 0.28 | 99.24 | 0.76 | 98 | 0.8 |
| **Sample 2** | | initial | <LOQ | 0.07 | 0.08 | 0.26 | 99.59 | 0.41 | 247 | 0.3 |
| | 5°C | 1 week | <LOQ | 0.02 | 0.03 | 0.26 | 99.70 | 0.30 | 248 | 1.3 |
| | | 2 weeks | <LOQ | 0.22 | 0.27 | 0.27 | 99.24 | 0.76 | 246 | 0.3 |
| | 25°C | 1 week | <LOQ | 0.02 | 0.03 | 0.26 | 99.69 | 0.31 | 248 | 0.9 |
| | | 2 weeks | <LOQ | 0.23 | 0.28 | 0.26 | 99.23 | 0.77 | 246 | 1.4 |
| LOQ = limit of quantification | | | | | | | | | | |

**[0405]** Solution stability studies were also performed, with samples stored at both 5°C and 25°C. Measurements were taken after 1 week and 2 weeks of storage. The results are shown in Table 8 below. The column with a retention time of 32.36 min correlates with the compound of Formula (I).

**Table 8. SDD solution stability data**

| **Retention time (min)** | | | 31.51 | 32.26 | |
|---|---|---|---|---|---|
| **Relative retention time** | | | 0.97 | 1.00 | |
| | **Storage temp** | **Timepoint** | | | **Total impurities** |
| **Ref. Std.** | | | 0.74 | 99.26 | 0.74 |
| **Formula (I)** | | | 0.26 | 99.74 | 0.26 |
| **Sample 1** | | initial | 0.33 | 99.67 | 0.33 |
| | 5°C | 2 weeks | 0.29 | 99.71 | 0.29 |
| | 25°C | 2 weeks | 0.38 | 99.62 | 0.38 |
| **Sample 2** | | initial | 0.25 | 99.75 | 0.25 |
| | 5°C | 2 weeks | 0.26 | 99.74 | 0.26 |
| | 25°C | 2 weeks | 0.33 | 99.67 | 0.33 |

**[0406]** Stability studies were also performed for the SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64, with samples stored at both 5°C (closed with desiccant), 25°C (60% RH, closed with desiccant), and 30°C (65% RH, closed with desiccant). Measurements were taken after storage for 1 month, 2 months, 3 months, 6 months, and 12 months. No change in purity was observed after 12 months of storage. The results are shown in Table 9 below. The column with a retention time of 30.2 min correlates with the compound of Formula (I).

**Table 9. SDD stability data**

| **Retention time (min)** | | | 28.7 | 30.2 | | |
|---|---|---|---|---|---|---|
| **Relative retention time** | | | 0.95 | 1.00 | | |
| | **Storage conditions** | **Timepoint** | | | **Total impurities** | **Potency (mgA/g)** |
| **Crystalline Formula (I)** | | | 0.26 | 99.74 | 0.26 | 1001 |

(continued)

| | Storage conditions | Timepoint | | | Total impurities | Potency (mgA/g) |
|---|---|---|---|---|---|---|
| **Sample 4 (25% Formula (I):75% PVP/VA 64)** | | initial | 0.26 | 99.74 | 0.26 | 245 |
| | 5°C (closed w/ desiccant) | 1 month | 0.25 | 99.75 | 0.25 | 247 |
| | | 2 months | 0.25 | 99.75 | 0.25 | 244 |
| | | 3 months | 0.26 | 99.74 | 0.26 | 246 |
| | | 6 months | 0.25 | 99.75 | 0.25 | 245 |
| | | 12 months | 0.25 | 99.75 | 0.25 | 248 |
| | 25°C/60% RH (closed with desiccant) | 1 month | 0.25 | 99.75 | 0.25 | 245 |
| | | 2 months | 0.25 | 99.75 | 0.25 | 247 |
| | | 3 months | 0.25 | 99.75 | 0.25 | 246 |
| | | 6 months | 0.25 | 99.75 | 0.25 | 242 |
| | | 12 months | 0.25 | 99.75 | 0.25 | 245 |
| | 30°C/65% RH (closed with desiccant) | 1 month | 0.25 | 99.75 | 0.25 | 249 |
| | | 2 months | 0.25 | 99.75 | 0.25 | 242 |
| | | 3 months | 0.25 | 99.75 | 0.25 | 246 |
| | | 6 months | 0.25 | 99.73 | 0.25 | 243 |
| | | 12 months | 0.25 | 99.75 | 0.25 | 242 |

**[0407]** While Samples 1 and 2 showed degradation after about 2 weeks of storage, the SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64 (Sample 4) was found to be both chemically and physically stable and was further screened and characterized as described below.

***25% Formula (I)/75% PVP/VA 64 SDD process parameter screening manufacture Round 1***

**[0408]** The 25% Formula (I)/75% PVP/VA 64 SDD was prepared on a Pharmaceutical Spray Dryer with 100 kg/hr drying gas capacity (PSD-1). The manufacturing summary is shown in Table 10, below.

**Table 10. Manufacturing summary of process parameters**

| **Formulation** | 25% Formula (I):75% PVP/VA 64 |
|---|---|
| **Solids Loading (wt%)** | 10 |
| **Batch Size (kg)** | 1.5 |
| **Solvent** | Acetone |
| **Atomizer (Pressure Swirl)** | SK 80-16 |
| **Solution Flow-rate (g/min)** | 160 |
| **Atomization Pressure (psig)** | 480 |
| **Inlet Temperature (°C)** | 94 |
| **Outlet Temperature (°C)** | 40 |
| **Calculated Outlet Acetone Saturation (% RS)** | 6.2 |
| **Dry Yield (%)** | 73 |

**[0409]** Based on the 73% yield observed in the first round of process screening, three sprays were performed to investigate the effect of reducing solution throughput and outlet temperature on product yield. All sprays were conducted

at a reduced flow-rate of 110 g/min. The outlet temperature was varied at 40°C (Lot A), 35°C (Lot B), and 30°C (Lot C). The outlet temperature was decreased while maintaining a low outlet acetone saturation to increase the difference between the chamber outlet temperature and the wet SDD $T_g$, thus improving product yields. The spray dryer chamber and outlet ductwork were cleaned between all manufactures. A manufacturing summary is shown in Table 11.

**Table 11. Manufacturing summary for process parameters (1.5 kg batch size)**

| Description | Low Flow-Rate | Low Flow-Rate/Low Outlet Temperature | Low Flow-Rate/Lower Outlet Temperature |
|---|---|---|---|
| **Lot** | A | B | C |
| **Solids Loading (wt%)** | 10 | 10 | 10 |
| **Batch Size (kg)** | 1.5 | 1.5 | 1.5 |
| **Solvent** | Acetone | Acetone | Acetone |
| **Atomizer (Pressure Swirl)** | Steinen A75 | Steinen A75 | Steinen A75 |
| **Solution Flow-Rate (g/min)** | 110 | 110 | 110 |
| **Atomization Pressure (psig)** | 275 | 285 | 285 |
| **Inlet Temperature (°C)** | 79 | 72 | 63 |
| **Outlet Temperature (°C)** | 40 | 35 | 30 |
| **Calculated Outlet Acetone Saturation (% RS)** | 4.3 | 5.2 | 6.4 |
| **Calculated wet SDD $T_g$ (°C)** | 72 | 71 | 69 |
| **Dry Yield (%)** | 55 | 80 | 43 |

**[0410]** The conditions used for Lot B were found to give the highest yield. One additional spray was then performed at the same processing conditions as Lot B while increasing the batch size from 1.5 kg to 3.5 kg to evaluate process consistency and to determine if product yield would continue to improve over time. The averaged process conditions for this lot are shown in Table 12.

**Table 12. Manufacturing summary of process parameters (1.5 kg and 3.5 kg batch sizes)**

| Description | Low Flow-Rate/Low Outlet Temperature | Low Flow-Rate/Low Outlet Temperature/Larger Batch Size |
|---|---|---|
| **Lot** | B | D |
| **Solids Loading (wt%)** | 10 | 10 |
| **Batch Size (kg)** | 1.5 | 3.5 |
| **Solvent** | Acetone | Acetone |
| **Atomizer (Pressure Swirl)** | Steinen A75 | Steinen A75 |
| **Solution Flow-Rate (g/min)** | 110 | 110 |
| **Atomization Pressure (psig)** | 285 | 285 |
| **Inlet Temperature (°C)** | 72 | 72 |
| **Outlet Temperature (°C)** | 35 | 35 |
| **Calculated Outlet Acetone Saturation (% RS)** | 5.2 | 5.2 |
| **Calculated wet SDD $T_g$ (°C)** | 71 | 71 |
| **Dry Yield (%)** | 80 | 84 |

**[0411]** The 1.5 kg batch size (Lot D) was sprayed with an 84% yield compared to the 80% yield of the 3.5 kg batch (Lot B).

***25% Formula (I)/75% PVP/VA 64 SDD process parameter screening characterisation***

**[0412]** The 25% Formula (I)/75% PVP/VA 64 SDDs manufactured to evaluate processing parameters were characterized for powder properties, performance, and physical and chemical properties. Testing included particle size distribution by Malvern, determination of bulk and tapped density, microcentrifuge dissolution, modulated differential scanning calorimetry (mDSC), powder x-ray diffraction (PXRD), scanning electron microscope (SEM), and assay and related substances. The results did not show any significant differences between the lots.

**[0413]** The particle size distribution (PSD) and tabulated powder properties data of the 25% Formula (I)/75% PVP/VA 64 SDDs are shown in Table 13. All 25% Formula (I)/75% PVP/VA 64 SDDs were observed to have a very similar PSD with a $D_{50}$ of approximately 16 μm. All 25% Formula (I)/75% PVP/VA 64 SDDs were observed to have low bulk and tapped densities.

**Table 13. Powder properties of process parameter screening PVP/VA-64 SDDs**

| Sample | Lot | $D_{10}$ (μm) | $D_{50}$ (μm) | $D_{90}$ (μm) | $D_{(3,2)}$ (μm) | $D_{(4,3)}$ (μm) | Span | Bulk density (g/mL) | Tapped density (g/mL) |
|---|---|---|---|---|---|---|---|---|---|
| 40°C Outlet | A | 5 | 15 | 34 | 8 | 17 | 1.93 | 0.12 | 0.25 |
| 35°C Outlet | B | 5 | 16 | 36 | 9 | 19 | 1.97 | 0.11 | 0.23 |
| 30°C Outlet | C | 5 | 15 | 32 | 7 | 17 | 1.86 | 0.12 | 0.27 |
| 35°C Outlet, 3.5 kg batch | D | 5 | 16 | 38 | 9 | 19 | 1.98 | 0.12 | 0.24 |

**[0414]** The 3.5 kg batch size lot was analyzed and compared to process parameter Lot A. Dissolution performance was similar for each of these lots. Dissolution was rapid to $C_{max}$ and high free drug was sustained through 90 minutes. These data are shown in Table 14.

**Table 14. Dissolution performance of Lot A (1.5 kg batch size) vs. Lot D (3.5 kg batch size)**

| Sample | $C_{max90}$ (μg/mL) | $AUC_{90}$ (min*μg/mL) | $C_{90}$ (μg/mL) | $Ultra_{90}$ (μg/mL) |
|---|---|---|---|---|
| Lot A | 447 | 37,740 | 437 | 319 |
| Lot D | 437 | 37,120 | 433 | 301 |

**[0415]** The 25% Formula (I)/75% PVP/VA 64 SDDs were also evaluated by DSC, PXRD, and SEM. The DSC thermograms showed a single $T_g$ at 84°C, indicating homogeneous dispersions. PXRD diffractograms showed no evidence of crystals in the SDDs. SEM images showed inflated sphere morphology with some broken particles and some very small particles.

**[0416]** Additional testing on Lot B was carried out, which included assessing the chemical/physical stability of both spray solution and SDD prior to secondary drying (wet SDD) to establish maximum in-process hold times. Residual acetone concentration as a function of secondary drying time in a convection tray dryer was also evaluated to nominate tray drying conditions to ensure the SDD is dried below International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for acetone.

**[0417]** Residual acetone content as a function of drying time was assessed by drying wet SDD in a tray dryer and collecting samples over a 24-hour period. Wet SDD was dried at 40°C/15% relative humidity (RH) and was observed to dry below ICH acetone guidelines (0.5 wt%, 5000 ppm) by four hours.

**[0418]** Spray solution hold time was determined by making up a representative solution that contained 2.5 wt% compound of Formula (I), 7.5 wt% PVP/VA 64, and 90 wt% acetone. These solutions were analyzed initially for related substances. and then aged at 5°C and 25°C. Aliquots were taken and analyzed for related substances periodically for 14 days. Results showed no change in impurity profile at either condition through 14 days.

**[0419]** Wet SDD was analyzed for impurities after storage at 5°C and 25°C for 1 and 2 weeks and compared to the impurity profiles of the ingoing compound of Formula (I) and the SDD that was secondarily dried immediately after spray drying. The impurity profiles were similar to that of the initial dried sample and the ingoing compound of Formula (I) through 2 weeks of storage.

**[0420]** The wet SDD stability samples were characterized for physical stability by DSC, PXRD, and SEM. DSC thermograms showed a single $T_g$ at 81°C, indicative of a homogeneous dispersion with no phase separation. The PXRD diffractograms did not show any evidence of crystals after storage at either condition. SEM images showed a typical morphology of mostly inflated spheres with some broken particles.

**Example 3: Preparation of a 1000 g batch of a spray-dried dispersion containing 25% of the compound of Formula (I) and 75% PVP/VA 64**

**[0421]** A 1000 g batch of the spray-dried dispersion containing 25% of the compound of Formula (I) and 75% PVP/VA 64 was prepared as described in Example 2 for the 1.5 kg and 3.5 kg batches. Briefly, acetone (90% (w/w) of the total mixture) was added to the mixing tank followed by the addition of 250.0 g of the compound of Formula (I) (2.5% (w/w) of the total mixture). The mixture was mixed for 30 minutes in the dark at a temperature range of 15°C to 27°C. At the end of the mixing period, the solution was clear and free of undissolved solids. The PVP/VA 64 (750.0 g, 7.5% (w/w) of the total mixture) was then added and the mixture was stirred for an additional 30 minutes in the dark at a temperature range of 15°C to 27°C. At the end of the mixing period, the solution was clear and free of undissolved solids.

**[0422]** The solution was pumped and atomized in a drying chamber. The spray-dried dispersions were prepared in a Pharmaceutical Spray Dryer with 100 kg/hr drying gas capacity (PSD-1). The inlet temperature was set at 75°C (varied between 60°C-90°C). The outlet temperature was set at 35°C (varied between 32°C-38°C). The feed pressure was set at 280 psig (varied between 230-330 psig). The feed rate was set at 110 g/min (varied between 90-130 g/min). The spray dried powder was then dried in a convection tray dryer with a bed depth of ≤ 2.5 cm at 40°C (±5°C) and 15% relative humidity (±10%) for 24 hours under amber light. The residual acetone after drying was < 0.5 wt% (5000 ppm). FIG. 5 is a flow diagram of the manufacturing process.

**Example 4: Preparation of spray-dried dispersion formulations of the compound of Formula (I) for clinical use**

**[0423]** The spray-dried dispersion (SDD) containing 25% compound of Formula (I) and 75% PVP/VA 64, prepared as described above, was formulated as a suspension or a capsule for clinical use.

***Suspension preparation***

**[0424]** A suspension that contained 50 mg of the SDD was prepared as follows. A 30 mL amber dosing bottle was tared on a balance. 200.0 mg SDD (50 mgA) ± 5% was then weighed into the dosing bottle. Using a 10-mL syringe, 5.0 mL of water (purified, USP) was added to the dosing bottle and the bottle was capped and shaken moderately for 30 seconds. The SDD suspension was stored in an amber vial at 2-8°C prior to use, and dosed within 24 hours of preparation.

***Capsule preparation***

**[0425]** An empty hard gelatin capsule, size 0 (Capsugel, Morristown, NJ), was placed on a balance and the weight was recorded. 200.0 mg SDD (50 mgA) ± 5% was then weighed onto weigh paper or an equivalent. All contents were transferred to the capsule using a ProFunnel device for Size 0 capsules. The filled capsule was placed on the balance and the weight was recorded. The weight of the empty capsule was subtracted from the filled weight, ensuring that the weight of the SDD within the capsule was 200.0 mg SDD ± 5%, or from 190.0 mg to 210.0 mg. The capsule was securely closed with the head, assuring it clicked into place. The capsules were stored in an amber vial at 2-8°C prior to use, and were dosed within 24 hours of preparation.

**Example 5: Dog relative bioavailability and food effect study**

**[0426]** Four spray-dried dispersions (SDDs), formulated in 0.25% methylcellulose as a suspension, were prepared: (1) 25% compound of Formula (I)/75% HPMCAS-L; (2) 10% compound of Formula (I)/90% HPMCAS-L; (3) 25% compound of Formula (I)/75% methyl methacrylate copolymer (1:1) (Eudragit® L100); and (4) 25% compound of Formula (I)/75% PVP/VA 64. A clinical capsule formulation was prepared as a reference formulation (Reference Formulation 1 from Table 5, above).

**[0427]** Dogs (two cohorts, six dogs in each) were dosed in six sessions, including fasted state sessions and fed sessions (high fat diet), with 50 mg dose of one of the SDDs or reference per dog in a 3-way crossover design. Each session had a 3-day washout in between. All formulations were well tolerated. The study design is shown in Table 15, below.

**Table 15. Study design**

| Cohort 1 | Session 1 (Fasted) | Session 2 (Fed) | Session 3 (Fasted) | Session 4 (Fed) | Session 5 (Fasted) | Session 6 (Fed) |
|---|---|---|---|---|---|---|
| **Dog 1001** | Reference | Reference | SDD 1 | SDD 1 | SDD 2 | SDD 2 |
| **Dog 1002** | Reference | Reference | SDD 1 | SDD 1 | SDD 2 | SDD 2 |
| **Dog 2001** | SDD 1 | SDD 1 | SDD 2 | SDD 2 | Reference | Reference |
| **Dog 2002** | SDD 1 | SDD 1 | SDD 2 | SDD 2 | Reference | Reference |
| **Dog 3001** | SDD 2 | SDD 2 | Reference | Reference | SDD 1 | SDD 1 |
| **Dog 3002** | SDD 2 | SDD 2 | Reference | Reference | SDD 1 | SDD 1 |
| | | | | | | |
| **Cohort 2** | **Session 1 (Fasted)** | **Session 2 (Fed)** | **Session 3 (Fasted)** | **Session 4 (Fed)** | **Session 5 (Fasted)** | **Session 6 (Fed)** |
| **Dog 4001** | Reference | Reference | SDD 3 | SDD 3 | SDD 4 | SDD 4 |
| **Dog 4002** | Reference | Reference | SDD 3 | SDD 3 | SDD 4 | SDD 4 |
| **Dog 5001** | SDD 3 | SDD 3 | SDD 4 | SDD 4 | Reference | Reference |
| **Dog 5002** | SDD 3 | SDD 3 | SDD 4 | SDD 4 | Reference | Reference |
| **Dog 6001** | SDD 4 | SDD 4 | Reference | Reference | SDD 3 | SDD 3 |
| **Dog 6002** | SDD 4 | SDD 4 | Reference | Reference | SDD 3 | SDD 3 |

**[0428]** The area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0-\infty}$), maximum plasma concentration ($C_{max}$), the apparent terminal half-life ($t_{½}$), and the time to achieve maximum plasma concentration ($t_{max}$) were calculated. Results are shown in Table 16, below, and in FIGS. 6A and 6B.

**Table 16. Pharmacokinetic results**

| Cohort | Form | Fasted [Mean (%CV)] | | Fed [Mean (%CV)] | | Ratio of Fed/Fasted [Mean (%CV)] | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (ng/mL) | $AUC_{inf}$ (hr*ng/mL) | $C_{max}$ (ng/mL) | $AUC_{inf}$ (hr*ng/mL) | $C_{max}$ | AUC |
| **1 (N=4) *** | **Ref** | 652 (55.5) | 5170 (69.4) | 3650 (19.5) | 20100 (22) | 6.9 (48) | 5.5 (69.2) |
| | **SDD 1** | 524 (62.7) | 2870 (62.9) | 5760 (25.6) | 22800 (14.6) | 15.4 (66.9) | 8 (89.6) |
| | **SDD 2** | 487 (45.7) | 3950 (26.4) | 4220 (27.4) | 18100 (26.8) | 16.5 (40.7) | 6.3 (34.6) |

(continued)

| Cohort | Form | Fasted [Mean (%CV)] | | Fed [Mean (%CV)] | | Ratio of Fed/Fasted [Mean (%CV)] | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (ng/mL) | $AUC_{inf}$ (hr*ng/mL) | $C_{max}$ (ng/mL) | $AUC_{inf}$ (hr*ng/mL) | $C_{max}$ | AUC |
| 2 (N=6) | Ref | 854 (40.2) | 5520 (59.1) | 4220 (27.4) | 18100 (26.8) | 5.8 (46.5) | 4.1 (49.2) |
| | SDD 3 | 453 (28.3) | 2830 (21.6) | 5320 (13.5) | 23800 (26.1) | 12.6 (30.3) | 8.6 (22.2) |
| | SDD 4 | 353 (20.1) | 1840 (21.9) | 3060 (20.7) | 17200 (20.5) | 8.9 (29.3) | 8.4 (46.1) |
| *Animals 2001 and 2002 were excluded from summary statistics due to emesis in all 3 fed sessions, which resulted in notably lower exposures | | | | | | | |

**[0429]** The results showed that $t_{1/2}$ and $t_{max}$ were similar among the formulations, and comparable between the fed and fasted states. Under the fed state with a high fat meal, exposures increased and inter-animal variability decreased. The food effect was more notable with the spray-dried dispersion formulations, especially for peak exposure ($C_{max}$).

**[0430]** Compared to the reference form, SDD 4 (25% compound of Formula (I)/75% PVP/VA 64) appeared to have lower inter-animal variability, lower exposures under the fasted state, and slightly lower $C_{max}$ but relatively comparable AUC in the fed state.

**Example 6: Phase 1 study to evaluate the pharmacokinetics, effect of food on pharmacokinetics, and safety of the compound of Formula (I) in healthy adult subjects**

**[0431]** The present study was designed to evaluate the pharmacokinetics (PK) of the compound of Formula (I) as well as to evaluate the effect of a fed condition on the PK of the compound of Formula (I). The 50 mg dose was chosen for this study because it was within the tested dose range in completed Phase 1 and Phase 2 trials and was well tolerated in those studies. The objectives of the study were: to evaluate the PK of the compound of Formula (I) 50 mg in healthy adult subjects; to evaluate the effect of food on the PK of the compound of Formula (I) 50 mg; and to evaluate the safety and tolerability of the compound of Formula (I) 50 mg.

**Study Design**

**[0432]** This was a Phase 1, open-label, randomized, 2-period crossover study of the PK and the effect of food on the PK of the compound of Formula (I) in 16 healthy male and female adult subjects, 18 to 55 years of age.

**[0433]** After providing informed consent, subjects were screened for eligibility to participate in the study up to 28 days prior to Day 1 of treatment period 1. Eligible subjects were admitted to the clinical unit on Day -1 and randomized to 1 of the 2 treatment sequences (16 subjects [8 males and 8 females]; see Table 17, below). On Day 1 of each treatment period, subjects received a single dose of the compound of Formula (I) 50 mg under fasted or fed conditions. There were 21 days between doses.

**Table 17. Treatment sequences**

| Treatment sequence | Treatment period I | Treatment period 2 |
|---|---|---|
| 1 | Formula (I) - fasted | Formula (I) - fed |
| 2 | Formula (I) - fed | Formula (I) - fasted |

**[0434]** Subjects were required to fast for at least 4 hours before check-in on Day -1. In the fasted condition, subjects were required to fast overnight for at least 10 hours prior to dosing and continued to fast for an additional 4 hours after dosing. In the fed condition, subjects were required to fast overnight for at least 10 hours and then ingest a liquid dietary supplement with study drug (liquid dietary supplement was consumed within 30 minutes) and not consume any other food for 4 hours after dosing. During both treatment periods, water was not permitted for 1 hour before dosing until 2 hours after dosing except for the water/liquid dietary supplement provided for study drug dosing. Vanilla-flavored Ensure Plus® was used as the liquid dietary supplement.

**[0435]** On Day 1 of each treatment period, subjects were dosed with the compound of Formula (I) 50 mg. Blood samples were collected for PK analysis over a period of 36 hours during the in-house stay. Subjects remained in the

unit on the day of dosing and were discharged on Day 2 of each treatment period, following completion of all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects returned to the clinical unit on an outpatient basis for PK blood sample collection and safety assessments. On Day 21 of treatment period 1, subjects arrived at the site and had Day 21 assessments completed in the evening, and they stayed overnight at the site and began Day 1 of treatment period 2 the following day. A final follow-up study visit was conducted on Day 22 of treatment period 2 (21 ± 2 days after treatment period 2 dosing) or upon early termination.

**[0436]** During each treatment period, blood samples for PK analysis were collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

**[0437]** Safety assessments (including clinical safety laboratory tests, vital sign measurements, physical examinations, and electrocardiograms (ECGs)) were conducted at scheduled times throughout the study. Adverse events (AEs) and the use of concomitant medications were monitored throughout the study. FIG. 7 illustrates the study design.

*Test **product,** dose **and mode of administration***

**[0438]** The compound of Formula (I) was supplied as an encapsulated, lipidic semi-solid containing 50 mg of the compound of Formula (I) as free base equivalent for oral administration. Subjects swallowed a single capsule with approximately 240 mL of water in the fasted condition. Subjects swallowed a single capsule with a liquid dietary supplement (Ensure Plus® [237 mL container]) with up to an additional 120 mL of water in the fed condition.

***Duration of treatment***

**[0439]** The duration of study participation for each adult subject was approximately 10 weeks, including up to 28 days of screening, 2 days of dosing separated by 21 days, and a final follow-up study visit 21 days after receiving the last dose of study drug during treatment period 2.

**Criteria for Evaluation**

***Pharmacokinetics***

**[0440]** The following plasma PK parameters were calculated for the compound of Formula (I):

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-tlast}}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours ($AUC_{0\text{-}24}$)
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration ($C_{max}$)
- Time to achieve maximum plasma concentration ($t_{max}$)
- Delay time between time of dosing and time of appearance of measurable test article ($T_{lag}$)
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant ($\lambda z$)
- Apparent mean residence time (MRT)
- Molar AUC ratio of the hydroxylated metabolite of the compound of Formula (I) to the parent drug the compound of Formula (I)

**[0441]** The following plasma PK parameters were calculated only for the compound of Formula (I):

- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

*Safety*

**[0442]** Safety was monitored throughout the study and included the following assessments:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiograms (ECGs)

***Statistical Methods***

**[0443]** Pharmacokinetic parameters were calculated using noncompartmental methods and summarized by condition (fed or fasted) using descriptive statistics. Two-sided 90% confidence intervals were calculated for the ratio under the fed condition vs. under the fasted condition for $AUC_{0-\infty}$, $AUC_{0\text{-tlast}}$, and $C_{max}$ for the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I).

**[0444]** Safety data were summarized with descriptive statistics.

**Pharmacokinetics**

***Pharmacokinetic** assessments*

**[0445]** PK plasma samples for analyses of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) were collected at the following times during each treatment period:

- Day 1: within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5,6, 7, 8, 9, 10, 12, and 16 hours after dosing.
- Day 2: approximately 24 and 36 hours after dosing.
- Day 8: approximately 168 hours after dosing.
- Day 15: approximately 336 hours after dosing.
- Approximately 504 hours after dosing (for treatment period 1, this sample was collected in the morning at least 30 minutes prior to the predose sample on Day 1 of treatment period 2).
- Final study visit for subjects who terminate early: 1 sample.

**[0446]** Blood samples on Day 1 were collected within 5 minutes of the scheduled sampling times (other than the predose sample). Blood samples on Days 2, 8, and 15 were collected within 2 hours of the scheduled sampling time. The 504 hour blood sample for treatment period 2 had a ± 2-day window. A PK sample was to be collected from subjects who terminated early. The exact time of sampling in hour and minutes was recorded.

***Bioanalytical methods***

**[0447]** Plasma samples were analyzed for the compound of Formula (I) and for its hydroxylated metabolite by in Ventiv Health, Princeton NJ, in compliance with Good Laboratory Practice (GLP) and relevant Standard Operating Procedures (SOPs).

**[0448]** The concentrations of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) were quantified in plasma samples according to validated methods using tandem mass spectrometry in positive ion mode. This method was validated for the analysis of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) in 25.0 μL dipotassium ethylenediaminetetraacetic acid ($K_2$-EDTA) human plasma samples over concentration ranges of 5.00 to 2500 ng/mL and 0.500 and 250 ng/mL, respectively. All analytical results were within acceptable limits. Incurred sample reanalysis (ISR) was successfully conducted in this study for both analytes.

Results

***Pharmacokinetic results***

**[0449]** Eight male and eight female subjects were enrolled. The mean age was 37.1 years (range, 21 to 55 years). The majority of subjects were White (93.8%) and of Hispanic ethnicity (81.3%). The mean weight at screening was 160.28 lbs (range, 102.0 to 222.2 lbs) and mean BMI was 25.50 kg/m$^2$ (range, 20.7 to 30.5 kg/m$^2$). The randomization was well balanced with respect to demographics and baseline characteristics.

**[0450]** All 16 subjects were included in the safety analysis set. No subjects were excluded from the safety analysis set and no subject had his or her PK data excluded from analysis.

**[0451]** The mean plasma concentration versus time profiles for the compound of Formula (I) under fasted and fed conditions are presented in FIGS. 8A and 8B, respectively. The compound of Formula (I) was slowly absorbed after oral administration in both fasted and fed conditions. Mean plasma concentrations were lower in the fasted than in the fed condition.

**[0452]** PK parameters for the compound of Formula (I) after treatment with the compound of Formula (I) under fasted and fed conditions are summarized in Table 18, below, where $AUC_{0-24}$=area under the plasma concentration vs. time curve from 0 to 24 hours, AUCo-$t_{bu}$t=AUC from 0 hours to last measurable concentration, $AUC_{0-\infty}$=AUC from 0 hours

extrapolated to infinity, CL/F=apparent systemic clearance after oral administration, CV=coefficient of variation, $C_{max}$=maximum plasma concentration, CV(%)=coefficient of variation, max=maximum, min=minimum, MRT=apparent mean residence time, PK=pharmacokinetic, SD=standard deviation, $t_{½}$=apparent terminal half-life, $T_{lag}$=delay time between time of dosing and time of appearance of measurable test article, $t_{max}$=time to maximum plasma concentration, VZ/F=apparent volume of distribution during the terminal phase after oral administration.

**[0453]** The PK data for $t_{max}$, $T_{lag}$, $t_{½}$, MRT, and Vz/F were rounded to 2 significant figures and all other parameters ($AUC_{0-24}$, $AUC_{0-tlast}$, $AUC_{0-\infty}$, $C_{max}$, and CL/F) were rounded to 3 significant figures. The last significant figure was rounded up if the digit to the right of it was ≥5, and was rounded down if the digit to the right of it was ≤4.

**Table 18. Summary of Formula (I) PK parameters (safety analysis set)**

| Parameter Statistic | Fasted Formula (I) (50 mg) (N=16) | Fed Formula (I) (50 mg) (N=15) |
|---|---|---|
| **$AUC_{0-24}$ (ng×hr/mL)** Mean (SD) Geometric CV% | 5590 (2230) 32.7 | 9950 (2540) 26.2 |
| **$AUC_{0-tlast}$ (ng×hr/mL)** Mean (SD) Geometric CV% | 8020 (5110) 53.6 | 16200 (5450) 39.7 |
| **$AUC_{0-\infty}$ (ng×hr/mL)** Mean (SD) Geometric CV% | 9440 (2990) [n=7] 39.7 | 17800 (4990) [n=12] 28.1 |
| **$C_{max}$ (ng/mL)** Mean (SD) Geometric CV% | 731 (301) 36.6 | 1550 (392) 24.2 |
| **$t_{max}$ (hours)** Median (min, max) | 6.0 (3.0, 6.0) | 5.0 (3.0, 6.0) |
| **$T_{lag}$ (hours)** Mean (SD) | 0.63 (0.22) | 0.94 (0.37) |
| **$t_{½}$ (hours)** Mean (SD) Geometric CV% | 33 (17) [n=7] 99 | 42 (6.8) [n=12] 15 |
| **MRT (hours)** Mean (SD) Geometric CV% | 28 (11) [n=7] 49 | 30 (5.0) [n=12] 16 |
| **CL/F (L/hr)** Mean (SD) Geometric CV% | 6.0 (2.7) [n=7] 40 | 3.0 (0.82) [n=12] 28 |
| **VZ/F (L)** Mean (SD) Geometric CV% | 240 (120) [n=7] 67 | 180 (57) [n=12] 30 |

**[0454]** As seen in Table 18, above, administration of the compound of Formula (I) 50 mg under fed compared with fasted conditions resulted in a higher mean $C_{max}$ of the compound of Formula (I) (approximately 2-fold higher; 1550 vs. 731 ng/mL), a longer $t_{½}$ (42 vs. 33 hours), a slightly shorter median $t_{max}$ (5.0 vs. 6.0 hours), and a higher mean $AUC_{0-\infty}$ (approximately 2-fold higher; 17800 vs. 9440 ngxhr/mL). The compound of Formula (I) geometric mean ratios for $C_{max}$ and $AUC_{0-tlast}$ for fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when administered with food. The upper and lower 90% confidence interval (CI) bounds for both $C_{max}$ (187.4% and 255.1%, respectively) and $AUC_{0-tlast}$ (182.9% and 253.1%, respectively) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure.

**[0455]** Frequency distribution of $T_{lag}$ and $t_{max}$ values are presented in Table 19 and Table 20, respectively. Spaghetti plots for the compound of Formula (I) $AUC_{0-tlast}$, $AUC_{0-\infty}$ and $C_{max}$ are shown in FIGS. 9A, 9B, and 9C, respectively.

**Table 19. Frequency distribution of plasma Formula (I) $T_{lag}$ values by treatment (safety analysis set)**

| $T_{lag}$ (hr) | Statistic | Fasted (Formula (I) 50 mg) (N=16) | Fed (Formula (I) 50 mg) (N=15) |
|---|---|---|---|
| 0.50 | n (%) | 11 (68.8%) | 3 (20.0%) |
| 0.53 | n (%) | 1 (6.3%) | 0 (0.0%) |
| 0.55 | n (%) | 0 (0.0%) | 1 (6.7%) |
| 1.00 | n (%) | 4 (25.0%) | 8 (53.3%) |
| 1.02 | n (%) | 0 (0.0%) | 1 (6.7%) |
| 1.03 | n (%) | 0 (0.0%) | 1 (6.7%) |
| 2.00 | n (%) | 0 (0.0%) | 1 (6.7%) |

**Table 20. Frequency distribution of plasma Formula (I) $T_{max}$ values by treatment (safety analysis set)**

| $T_{max}$ (hr) | Statistic | Fasted (Formula (I) 50 mg) (N=16) | Fed (Formula (I) 50 mg) (N=15) |
|---|---|---|---|
| 3.00 | n (%) | 1 (6.3%) | 2 (13.3%) |
| 4.02 | n (%) | 1 (6.3%) | 0 (0.0%) |
| 5.00 | n (%) | 4 (25.0%) | 8 (53.3%) |
| 5.03 | n (%) | 0 (0.0%) | 1 (6.7%) |
| 5.05 | n (%) | 0 (0.0%) | 1 (6.7%) |
| 6.00 | n (%) | 10 (62.5%) | 2 (13.3%) |
| 6.02 | n (%) | 0 (0.0%) | 1 (6.7%) |

**[0456]** The compound of Formula (I) was slowly absorbed after oral administration in the fasted and fed conditions. In the fasted condition, the mean compound of Formula (I) $C_{max}$ was approximately 53% lower than in the fed condition (731 vs. 1550 ng/mL). Due to a prolonged elimination phase, $t_{½}$ values and therefore, $AUC_{0-\infty}$ values could not be determined for some the compound of Formula (I) concentration-time profiles. Mean $AUC_{0-\infty}$ was approximately 47% lower in the fasted condition than in the fed condition (9440 vs. 17800 ngxhr/mL) for those subjects for whom $AUC_{0-\infty}$ could be determined. Mean $AUC_{0-tlast}$ was approximately 50% lower in the fasted condition than in the fed condition (8020 vs. 16200 ngxhr/mL). Median $t_{max}$ was slightly longer in the fasted condition than in the fed condition (6.0 vs. 5.0 hours) and mean $t_{½}$ was shorter in the fasted condition than in the fed condition (33 vs. 42 hours) for those subjects for whom a $t_{½}$ could be determined. Variability in the compound of Formula (I) PK (geometric CV%) for AUC, $C_{max}$, $t_{½}$, and MRT was lower in the fed condition compared with the fasted condition.

**[0457]** The geometric mean ratios and associated 90% CIs for $AUC_{0-tlast}$ and $C_{max}$ for the compound of Formula (I) after treatment with the compound of Formula (I) for the fed vs. fasted condition are provided in Table 21, below, where $AUC_{0-tlast}$= AUC from 0 hours to last measurable concentration, $C_{max}$=maximum plasma concentration, and PK=pharmacokinetic.

**Table 21. Formula (I) geometric mean ratios for PK exposure parameters under fed vs. fasted conditions (safety analysis set)**

| Parameter | Ratio[a] (%) (Fed vs. Fasted Condition) | 90% Confidence Interval[b] |
|---|---|---|
| $AUC_{0-tlast}$ (ngxhr/mL) | 215.2 | 182.9,253.1 |
| $C_{max}$ (ng/mL) | 218.6 | 187.4,255.1 |
| [a] Ratio of geometric least-squares means was based on a mixed model using log-transformed (base 10) data. [b] The 90% confidence interval for geometric mean ratio was based on least-squares means using log-transformed (base 10) data. | | |

**[0458]** The compound of Formula (I) geometric mean ratios for $C_{max}$ and $AUC_{0-tlast}$ for the fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when administered with food. The upper and lower 90% CI bounds for both $C_{max}$ (187.4%, 255.1%) and $AUC_{0-tlast}$ (182.9%, 253.1%) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure. Due to the missing $AUC_{0-\infty}$ values, the food effect on overall exposure was not assessed using $AUC_{0-\infty}$ values.

***Conclusion***

**[0459]** Administration of the compound of Formula (I) 50 mg under fed compared with fasted conditions resulted in a higher mean $C_{max}$ of the compound of Formula (I) (approximately 2-fold higher; 1550 vs. 731 ng/mL), a longer $t_{½}$ (42 vs. 33 hours), a slightly shorter median $t_{max}$ (5.0 vs. 6.0 hours), and a higher mean $AUC_{0-\infty}$ (approximately 2-fold higher; 17800 vs. 9440 ngxhr/mL). The compound of Formula (I) geometric mean ratios for $C_{max}$ and $AUC_{0-tlast}$ for fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approx-

imately 2-fold greater when administered with food. The upper and lower 90% CI bounds for both $C_{max}$ (187.4%, 255.1%) and $AUC_{0\text{-tlast}}$ (182.9%, 253.1%) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure. Similar results were observed with the hydroxylated metabolite of the compound of Formula (I). Overall, these results indicate that the compound of Formula (I) 50 mg was well tolerated in healthy subjects when administered under fasted or fed conditions and that the total AUC and $C_{max}$ were increased when the compound of Formula (I) was taken with food.

**Example 7: Phase 1 study to evaluate the relative bioavailability, effect of food on pharmacokinetics, and safety of formulations of the compound of Formula (I) in healthy adult subjects**

**[0460]** A Phase 1 study to compare the relative bioavailability of a 50 mg dose of different formulations of the compound of Formula (I) as well as to evaluate the effect of fasting and fed conditions on the pharmacokinetics (PK) of the compound of Formula (I) was designed. The 50 mg dose was chosen for this study because it is within the tested dose range in completed Phase 1 and Phase 2 trials and was well tolerated in those studies. The objectives of the study are: to evaluate the PK and compare the relative bioavailability of the compound of Formula (I) 50 mg formulations in healthy adult subjects; to evaluate the effect of food on the PK of the compound of Formula (I) 50 mg formulations; and to evaluate the safety and tolerability of the compound of Formula (I) 50 mg formulations.

**Study Design**

**[0461]** This is a Phase 1, open-label, randomized, three-period crossover study of the relative bioavailability and the effect of food on the PK of the compound of Formula (I) 50 mg in healthy adult subjects. During treatment period 1 and treatment period 2, subjects will receive a single dose of the compound of Formula (I) 50 mg administered as an encapsulated, lipidic semi-solid (reference) and 1 of 2 different spray-dried dispersion (SDD) test formulations (suspension or capsule) under fed conditions, and during treatment period, three subjects will receive the same SDD test formulation under fasted conditions.

**[0462]** A total of 36 healthy adult subjects will be randomized to 1 of 4 treatment sequences (9 subjects per sequence; approximately equal distribution of males and females per sequence; see Table 22, below). There will be 21 days between each dose.

**Table 22. Treatment sequences**

| Treatment sequence | Treatment period 1 (Fed) | Treatment period 2 (Fed) | Treatment period 3 (Fasted) |
|---|---|---|---|
| 1 | Reference | SDD suspension | SDD suspension |
| 2 | SDD suspension | Reference | SDD suspension |
| 3 | Reference | SDD capsule | SDD capsule |
| 4 | SDD capsule | Reference | SDD capsule |

**[0463]** After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days prior to Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1, and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During treatment periods 1 and 2, subjects will fast overnight for at least 10 hours and then ingest a liquid dietary supplement (vanilla-flavored Ensure Plus®, 237 mL container) with the study drug and not consume any other food for 4 hours after dosing. During treatment period 3, subjects will fast overnight for at least 10 hours prior to dosing and continue to fast for an additional 4 hours after dosing. During all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water/liquid dietary supplement provided for study drug dosing.

**[0464]** On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 50 mg and have blood samples collected for PK analysis. Subjects will complete a taste satisfaction questionnaire after study drug ingestion on Day 1 of treatment period 3 (only for subjects who receive the SDD suspension under the fasted condition). Subjects will remain in the unit on the day of dosing and will be discharged on Day 2 of each treatment period, following completion of all required procedures, including collection of the 36-hour PK sample. On the mornings of Days 8 and 15 of each treatment period, subjects will return to the clinical unit on an outpatient basis for PK blood sample collection and safety assessments. On Day 21 of treatment period 1 and treatment period 2, subjects will arrive at the site and have Day 21 assessments completed, and they will stay overnight at the site and begin Day 1 of treatment period 2 or treatment period 3 the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 3 (21 $\pm$ 2 days after treatment period 3 dosing) or upon early termination.

**[0465]** Blood samples for PK analysis and safety assessments will be collected/conducted at scheduled times throughout the study. The study design schematic is shown in FIG. 10.

***Duration of treatment***

**[0466]** The expected duration of study participation for each healthy adult subject will be approximately 13 weeks, including up to 28 days of screening, 3 doses each separated by 21 days, and a final follow-up study visit 21 days after receiving the last dose of study drug during treatment period 3.

*Test* ***product,*** *dose,* ***and mode*** *of* ***administration***

**[0467]** The compound of Formula (I) will be supplied as two different test formulations for oral administration: as powder in bottles for constitution into a suspension (20 mL) and as powder-filled capsules. The compound of Formula (I) test formulations will contain 50 mg of the compound of Formula (I) as free base equivalent. Subjects must swallow the study drug with a liquid dietary supplement (Ensure Plus® [237 mL container]) with an additional 100 mL of water (SDD capsule formulation) or with an additional 80 mL of water (SDD suspension formulation) during treatment period 1 or 2. Subjects must swallow the study drug with 330 mL of water (SDD capsule formulation) or 310 mL of water (SDD suspension formulation) during treatment period 3.

***Reference therapy, dose, and mode of administration***

**[0468]** The compound of Formula (I) reference formulation (encapsulated, lipidic semi-solid formulation) will be supplied as capsules for oral administration. The compound of Formula (I) reference capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. Subjects must swallow a single capsule with a liquid dietary supplement (Ensure Plus [237 mL container]) with an additional 100 mL of water during treatment period 1 or 2.

**Criteria for Evaluation**

***Pharmacokinetics***

**[0469]** Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

**[0470]** The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to the time of the last measurable concentration ($AUC_{0\text{-}tlast}$)
- Area under the plasma concentration curve extrapolated from 0 hours to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration ($C_{max}$)
- Time to achieve maximum plasma concentration ($t_{max}$)
- Delay time between time of dosing and time of appearance of measurable test article ($T_{lag}$)
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant ($\lambda z$)
- Apparent mean residence time (MRT)
- Molar AUC ratio of primary metabolite(s) to the parent drug the compound of Formula (I)

**[0471]** The following plasma PK parameters will be calculated only for the compound of Formula (I):

- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

***Other assessment***

**[0472]** A taste satisfaction questionnaire will be administered.

*Safety* ***assessments***

**[0473]** Safety will be monitored throughout the study and will include the following assessments:

- AEs
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiogram (ECG)

***Statistical methods***

**[0474]** Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by formulation using descriptive statistics. Two-sided 90% confidence intervals will be calculated for the ratio of each test formulation (SDD suspension and SDD capsule) vs. the reference formulation for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and $C_{max}$ for the compound of Formula (I) and metabolites under fed conditions. Further, two-sided 90% confidence intervals will be calculated for the ratio of each test formulation under fasted conditions vs. under fed conditions for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and $C_{max}$ for the compound of Formula (I) and metabolites.

**[0475]** Safety and taste satisfaction questionnaire data will be summarized with descriptive statistics.

Results

***Pharmacokinetic results***

**[0476]** Pharmacokinetic results are shown in Tables 23-26, below.

**Table 23: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set - SDD Suspension Group)**

| | | Compound of Formula (I) Plasma Concentration | |
|---|---|---|---|
| **Parameter (units) Statistic** | **Reference Capsule (Fed) (N=18)** | **SDD Suspension (Fed) (N=18)** | **SDD Suspension (Fasted) (N=18)** |
| **$AUC_{0-tlast}$ (ng×hr/mL)** | | | |
| Mean (SD) | 16600 (7880) | 5980 (3960) | 737 (417) |
| Geom CV(%) | 46.8 | 72.8 | 68.7 |
| **$AUC_{0-\infty}$ (ng×hr/mL)** | | | |
| Mean | 17400 (8010) | 6500 (4180) | 893 (480) |
| Geom CV(%) | 45.4 | 71.7 | 60.1 |
| **$C_{max}$ (ng/mL)** | | | |
| Mean (SD) | 1480 (506) | 672 (323) | 72.3 (44.9) |
| Geom CV(%) | 32.1 | 57.9 | 57.5 |
| **$t_{max}$ (hr)** | | | |
| Median (min, max) | 5.0 (3.0, 6.0) | 5.0 (5.0, 10) | 7.0 (5.0, 12) |
| **$T_{lag}$ (hr)** | | | |
| Mean (SD) | 1.0 (0.31) | 0.85 (0.29) | 1.2 (0.65) |
| **$t_{½}$ (hr)** | | | |
| Mean (SD) | 50 (20) | 19 (6.1) | 9.0 (0.46) |
| Geom CV(%) | 140 | 93 | 23 |
| **MRT (hr)** | | | |
| Mean (SD) | 36 (43) | 23 (24) | 17 (2.9) |
| Geom CV(%) | 84 | 62 | 18 |
| **CL/F (L/hr)** | | | |

(continued)

| | | Compound of Formula (I) Plasma Concentration | |
|---|---|---|---|
| **Parameter (units) Statistic** | **Reference Capsule (Fed) (N=18)** | **SDD Suspension (Fed) (N=18)** | **SDD Suspension (Fasted) (N=18)** |
| Mean (SD) | 3.4 (1.4) | 11 (8.0) | 80 (54) |
| Geom CV(%) | 45 | 72 | 63 |
| **Vz/F (L)** | | | |
| Mean (SD) | 180 (260) | 210 (140) | 970 (560) |
| Geom CV(%) | 93 | 77 | 53 |
| **$T_{last}$ (hr)** | | | |
| Mean (SD) | 170 (140) | 77 (110) | 31 (7.6) |
| Geom CV(%) | 120 | 92 | 30 |

**Table 24: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set - SDD Suspension Group)**

| Analyte Parameter (units) | Treatment Comparison | Ratio (%) | 90% CI |
|---|---|---|---|
| **Compound of Formula (I)** | | | |
| $AUC_{0\text{-}tlast}$ (ngxhr/mL) | SDD Suspension (Fed) vs. Reference Capsule (Fed) | 32.2 | (26.4%, 39.4%) |
| $AUC_{0\text{-}\infty}$ | SDD Suspension (Fed) vs. Reference Capsule (Fed) | 33.5 | (27.7%, 40.6%) |
| $C_{max}$ (ng/mL) | SDD Suspension (Fed) vs. Reference Capsule (Fed) | 42.2 | (34.8%, 51.2%) |
| $AUC_{0\text{-}tlast}$ (ngxhr/mL) | SDD Suspension (Fasted) vs. Reference Capsule (Fed) | 4.4 | (3.4%, 5.7%) |
| $AUC_{0\text{-}\infty}$ | SDD Suspension (Fasted) vs. Reference Capsule (Fed) | 5.0 | (3.8%, 6.5%) |
| $C_{max}$ (ng/mL) | SDD Suspension (Fasted) vs. Reference Capsule (Fed) | 4.5 | (3.8%, 5.4%) |

**Table 25: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set - SDD Capsule Group)**

| | | Compound of Formula (I) Plasma Concentration | |
|---|---|---|---|
| **Parameter (units) Statistic** | **Reference Capsule (Fed) (N=18)** | **SDD Capsule (Fed) (N=18)** | **SDD Capsule (Fasted) (N=17)** |
| **$AUC_{0\text{-}tlast}$ (ng×hr/mL)** | | | |
| Mean (SD) | 19500 (7960) | 9470 (4670) | 1840 (1650) |
| Geom CV (%) | 50.4 | 48.0 | 78.7 |
| **$AUC_{0\text{-}\infty}$ (ng×hr/mL)** | | | |
| Mean | 20100 (7850) | 10000 (4610) | 2120 (1830) |
| Geom CV (%) | 47.1 | 44.9 | 73.7 |

(continued)

| | | Compound of Formula (I) Plasma Concentration | | |
|---|---|---|---|---|
| **Parameter (units) Statistic** | | **Reference Capsule (Fed) (N=18)** | **SDD Capsule (Fed) (N=18)** | **SDD Capsule (Fasted) (N=17)** |
| **$C_{max}$ (ng/mL)** | | | | |
| | Mean (SD) | 1770 (494) | 1110 (449) | 143 (110) |
| | Geom CV (%) | 25.7 | 44.5 | 74.1 |
| **$t_{max}$ (hr)** | | | | |
| | Median (min,max) | 5.0 (5.0, 8.0) | 5.0 (3.0, 6.0) | 7.0 (6.0, 12) |
| **$T_{lag}$ (hr)** | | | | |
| | Mean (SD) | 1.0 (0.38) | 1.3 (0.49) | 1.2 (0.88) |
| **$t_{½}$ (hr)** | | | | |
| | Mean (SD) | 35 (18) | 26 (20) | 14 (11) |
| | Geom CV (%) | 69 | 98 | 49 |
| **MRT (hr)** | | | | |
| | Mean (SD) | 28 (12) | 25 (14) | 21 (9.2) |
| | Geom CV (%) | 45 | 55 | 31 |
| **CL/F (L/hr)** | | | | |
| | Mean (SD) | 3.0 (1.5) | 5.9 (2.4) | 36 (18) |
| | Geom CV (%) | 47 | 45 | 74 |
| **Vz/F (L)** | | | | |
| | Mean (SD) | 130 (61) | 190 (140) | 630 (380) |
| | Geom CV (%) | 47 | 75 | 72 |
| **$T_{last}$ (hr)** | | | | |
| | Mean (SD) | 170 (96) | 100 (89) 44 (32) | |
| | Geom CV (%) | 91 | 100 | 39 |

**Table 26: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set - SDD Suspension Group)**

| **Analyte Parameter (units)** | **Treatment Comparison** | **Ratio (%)** | **90% CI** |
|---|---|---|---|
| **Compound of Formula (I)** | | | |
| $AUC_{0\text{-tlast}}$ | SDD Capsule (Fed) vs. Reference Capsule (Fed) | 48.2 | (41.4%, 56.1%) |
| $AUC_{0\text{-}\infty}$ (ngxhr/mL) | SDD Capsule (Fed) vs. Reference Capsule (Fed) | 49.7 | (43.1%, 57.2%) |

(continued)

| Analyte Parameter (units) | Treatment Comparison | Ratio (%) | 90% CI |
|---|---|---|---|
| **Compound of Formula (I)** | | | |
| $C_{max}$ (ng/mL) | SDD Capsule (Fed) vs. Reference Capsule (Fed) | 59.8 | (51.7%, 69.2%) |
| $AUC_{0\text{-tlast}}$ (ngxhr/mL) | SDD Capsule (Fasted) vs. Reference Capsule (Fed) | 8.0 | (5.7%, 11.2%) |
| $AUC_{0\text{-}\infty}$ (ngxhr/mL) | SDD Capsule (Fasted) vs. Reference Capsule (Fed) | 9.0 | (6.6%, 12.4%) |
| $C_{max}$ (ng/mL) | SDD Capsule (Fasted) vs. Reference Capsule (Fed) | 6.7 | (4.9%, 9.2%) |

**Example 8: Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia**

**[0477]** A Phase 2 study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of the compound of Formula (I) in adult subjects with classic congenital adrenal hyperplasia (CAH) was designed. The objectives of the study are: to assess the safety and tolerability of two ascending doses of the compound of Formula (I) in adult subjects with CAH; to evaluate the effect of repeated doses of the compound of Formula (I) on endogenous levels of PD biomarkers in adult subjects with CAH; and to evaluate plasma exposures following repeated doses of the compound of Formula (I) administered nightly.

**[0478]** The lower dose strength selected for this study, the compound of Formula (I) 50 mg, was well tolerated in both single and repeat-dose safety and PK studies in healthy volunteers. Doses up to 100 mg were also well tolerated in both single-dose and repeat-dose Phase 1 studies in healthy volunteers, and importantly, in a large Phase 2 study in non-elderly female and male subjects with major depressive disorder receiving the compound of Formula (I) during an 8-week, double-blind treatment period. Furthermore, the anticipated steady state exposures with the selected the compound of Formula (I) doses, using the predicted $C_{max}$ and AUC, are within the acceptable safety margins defined by the nonclinical toxicology studies that have been conducted to date.

**Study Design**

**[0479]** A Phase 2, open-label, multiple-dose, dose-escalation study to assess the safety, tolerability, PK, and PD of the compound of Formula (I) in approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH was designed. The study will include a sequential-cohort design with four compound of Formula (I) dose cohorts: 50 mg and 100 mg, with each dose administered for 14 consecutive days:

- Cohort 1: compound of Formula (I) 50 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 2: compound of Formula (I) 100 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 3: compound of Formula (I) 100 mg once daily with the evening meal at approximately 1900 hours.
- Cohort 4: compound of Formula (I) 100 mg twice daily with breakfast at approximately 0700 hours and with the evening meal at approximately 1900 hours.

**[0480]** There will be an approximate 2-week period to evaluate safety and tolerability data before proceeding from Cohort 1 to Cohort 2. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects). Table 27 below depicts the dose cohorts, doses, and number of subjects per cohort.

**Table 27. Dose cohorts, doses, and number of subjects**

| Cohort | Compound of Formula (I) Dose | Approximate Dosing Time(s) | Number of Subjects |
|---|---|---|---|
| 1 | 50 mg | 2200 hours | 8-10 |
| 2 | 100 mg | 2200 hours | 8-10 |

(continued)

| Cohort | Compound of Formula (I) Dose | Approximate Dosing Time(s) | Number of Subjects |
|---|---|---|---|
| 3 | 100 mg | 1900 hours | 8-10 |
| 4 | 100 mg | 0700 and 1900 hours | Up to 8 |

**[0481]** Subjects will be screened for eligibility to participate in the study for up to approximately 3 weeks (Days -28 to -8). Subjects who reenroll and have had a stable medication regimen for CAH since their last visit in this study do not have to undergo screening; those who reenroll and have had a change to their medication regimen for CAH must undergo a second screening visit. During screening, subjects will provide a single blood sample in the morning between 0700 and 1000 hours (prior to first morning dose of hydrocortisone) to determine their 17-hydroxyprogesterone (17-OHP) levels for study entry.

**[0482]** Eligible subjects who have a screening 17-OHP level ≥1,000 ng/dL will be admitted to the study center for 1 night and have baseline serial PD samples collected over a 24-hour period beginning in the evening of Day -7. Baseline serial PD samples will be collected at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

**[0483]** Subjects within each dose cohort will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for CYP21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (the compound of Formula (I) 50 or 100 mg) will be administered at approximately 2200 hours for Cohorts 1 and 2 and at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours for Cohorts 3 and 4. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

**[0484]** Subjects in Cohorts 1 and 2 will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for cytochrome P450 (CYP) 21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (compound of Formula(I) 50 mg or 100 mg) will be administered at approximately 2200 hours. The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 12-hour post-dose PK/PD samples are collected (at approximately 1000 hours) on Day 2 and after the 16-hour post-dose PK/PD samples are collected (at approximately 1400 hours) on Day 15. Subjects will be discharged from the study center the evening on Days 2 and 15 following completion of all study-related procedures for those days. Prior to this discharge on Day 2, study drug will be administered at the study center at approximately 2200 hours. Study drug will then be selfadministered nightly at home at approximately 2200 hours on Days 3 to 13. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 3 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center.

**[0485]** Subjects in Cohorts 3 and 4 will have a blood sample collected on Day 1 for CYP21A2 genotyping (only for subjects who have not previously participated in Cohorts 1 or 2). Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. For Cohort 3, study drug (compound of Formula(I) 100 mg) will be administered at home on Days 1 to 13 at approximately 1900 hours with each subject's evening meal. For Cohort 4, study drug compound of Formula(I) 100 mg) will be administered at home on Days 2 to 14 at approximately 0700 hours with each subject's breakfast and on Days 1 to 13 at approximately 1900 hours with each subjects' evening meal. For both cohorts, the Day 14 evening dose will be administered at the study site. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 1 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center. Subjects will be admitted to the study center on Day 14 (last day of dosing). On Day 14, subjects will receive study drug in the study center at approximately 1900 hours with a standard (moderate fat/moderate calorie) evening meal. The subjects' usual morning dose of concurrent steroidal treatments will be administered after PK/PD samples are collected at approximately 1400 hours on Day 15. Subjects will be discharged from the study center the evening on Day 15 following completion of all study-related procedures.

**[0486]** For all cohorts, follow-up visits on Days 21, 28, and 35 will be conducted at the study center or the subject's home by a qualified home healthcare provider (based on the subject's preference). A final study visit will be conducted at the study site approximately 5 weeks after the last dose of study drug (on Day 49 or early termination). There will be a visit window of - 8 hours for Day 7, -8 hours/+3 days for Days 21, 28, and 35, and +7 days for the final study visit. Safety, tolerability, PK, and PD will be assessed at scheduled times throughout the study. The study design schematic is shown in FIG. 11.

*Dose **escalation procedure***

**[0487]** Cohort 1 will consist of approximately 8 to 10 subjects who will receive a daily dose of the compound of Formula (I) 50 mg at approximately 2200 hours for 14 days (subjects will receive study drug at the site on Days 1, 2, and 14, and self-administer study drug at home on Days 3 to 13). Following the completion of Day 15 assessments for all subjects in the Cohort 1, a medical monitor will review the accumulated safety and tolerability results to ensure there are no safety concerns with proceeding to the 100 mg dose (Cohorts 2 and 3), and to determine if a maximum tolerated dose (MTD) has been reached. If the MTD is reached, no dose escalation will occur. There will be an approximate 2-week period between Cohorts 1 and 2 to accommodate this safety review. A similar procedure will be used prior to proceeding to the 100 mg twice daily dose (Cohort 4).

**[0488]** If the medical monitor determines that it is safe to proceed to the compound of Formula (I) 100 mg, subjects in Cohort 2 will be administered the compound of Formula (I) 100 mg daily for 14 days. Dosing for Cohorts 3 and 4 may begin simultaneously with Cohort 2.

**[0489]** During the 14-day dosing period for any cohort, dosing may be postponed or halted if one or more subjects experience a severe or serious adverse event (AE), or if the type, frequency, or severity of AEs becomes unacceptable. If dosing is postponed, the medical monitor will review all available safety, tolerability, and PK data before allowing any further subjects to receive study drug.

***Study Population***

**[0490]** Approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21 -hydroxylase deficiency CAH, who meet all protocol eligibility criteria, will be enrolled. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects).

***Duration** of **treatment***

**[0491]** The expected duration of study participation for each subject is approximately 11 weeks, including up to approximately 3 weeks for screening, a 24-hour PD baseline period (approximately 7 days prior to the first day of dosing), 14 days of dosing, and a follow-up period of approximately 5 weeks. The total duration of the study will be an additional 8 to 11 weeks for subjects who reenroll.

***Test product, dose, and mode** of **administration***

**[0492]** The compound of Formula (I) will be supplied as capsules containing 50 mg of the compound of Formula (I) free base for oral administration (see, e.g., Reference 1 formulation as described in Example 9). Doses of the compound of Formula (I) are 50 mg and 100 mg, administered in oral capsule form. Each dose of study drug for Cohorts 1 and 2 is to be administered with a bottle of vanilla-flavored Ensure Plus® (~237 mL). Each dose of study drug for Cohort 3 is to be administered with each subject's evening meal at approximately 1900 hours. Each dose of study drug for Cohort 4 is to be administered with each subject's breakfast at approximately 1900 hours (i.e., a total daily dose of 200 mg).

**Criteria for Evaluation**

*Cohorts 1 and 2*

**[0493]** Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 1 to 2 and Days 14 to 15 at: 15 minutes pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours post-dose; Day 7 (at approximately 24 hours post-dose); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours post-dose); and at the final study visit (Day 49 or early termination).

*Cohorts 3 and 4*

**[0494]** Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 14 to 15 at the following times (for Cohort 4, all times are relative to evening dosing unless otherwise indicated): 15 minutes predose and at 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 23, 24, and 27 hours postdose; Day 7 (at 24 hours postdose for Cohort 3 or at 12

hours post morning dose but prior to the evening dose for Cohort 4); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours postdose); and at the final study visit (Day 49 or early termination).

***Pharmacokinetics***

**[0495]** The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-}tlast}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours ($AUC_{0\text{-}24}$)
- Maximum plasma concentration ($C_{max}$)
- Time to maximum plasma concentration ($t_{max}$)
- Delay time between time of dosing and time of appearance of measurable test article ($T_{lag}$)
- Terminal half-life ($t_{½}$)
- Apparent terminal rate constant ($\lambda z$)
- Apparent mean residence time (MRT)

**[0496]** Additional PK parameters for Day 14 only:

- Average plasma concentration at steady state ($C_{avg}$)
- Percent fluctuation at steady state (% fluctuation)
- Accumulation index at steady state
- Apparent systemic clearance after oral administration (CL/F) (the compound of Formula (I) only)

***Pharmacodynamics***

**[0497]** Primary: Morning 17-OHP (serum; ng/dL) from the 0600, 0800, and 1000 hour samples (8-, 10-, and 12-hour post-dose samples from Cohorts 1 and 2 and 11-, 13-, and 15-hour postdose samples from Cohorts 3 and 4.

**[0498]** Secondary: 17-OHP at all other times, androstenedione (serum; ng/dL), testosterone (serum; ng/dL), cortisol (serum; μg/dL), and adrenocorticotropic hormone (plasma ACTH; pg/mL).

***Safety***

**[0499]** Safety and tolerability will be monitored throughout the study and will include the following assessments:

- Adverse events
- Clinical laboratory tests - clinical chemistry (including creatine kinase, myoglobin, total and conjugated bilirubin), hematology, coagulation (prothrombin time, aPTT, d-dimer, fibrinogen), and urinalysis (including quantitative myoglobin, casts and crystals)
- Vital signs
- Physical examinations (including musculoskeletal exam)
- 12-lead electrocardiograms (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Brief Psychiatric Rating Scale (BPRS)

***Statistical methods***

**[0500]** Safety, PK, and PD variables will be summarized within each dose cohort (the compound of Formula (I) 50 mg and 100 mg) using descriptive statistics. Summaries of PD measures will include both observed values and changes from pre-dose.

**Results**

*Pharmacokinetic results*

**[0501]** Eight subjects (four female and four male) were enrolled in this study and completed Cohort 1. Age, sex, and BMI information for the study participants is shown in Table 28, below.

**Table 28. Cohort 1 Subjects**

| Subject ID | Age (years) | Sex (Male/Female) | BMI (kg/m$^2$) |
|---|---|---|---|
| 001 | 37 | Female | 24.9 |
| 002 | 25 | Female | 32.0 |
| 003 | 49 | Male | 37.2 |
| 004 | 36 | Male | 25.0 |
| 005 | 27 | Female | 25.5 |
| 006 | 19 | Male | 21.7 |
| 007 | 25 | Male | 27.5 |
| 008 | 31 | Female | 34.4 |

**[0502]** The subjects received a daily dose of the compound of Formula (I) at 50 mg at approximately 2200 hours (~10 p.m. or bedtime) for 14 days. Arithmetic mean values for ACTH (FIG. 12A) and 17-OHP (FIG. 12B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, Day 1, and Day 14. Both ACTH and 17OHP concentration profiles at day 1 and day 14 show clear reductions from the baseline mean profiles. Cohort 1 mean PK parameters of $T_{max}$, $C_{max}$, and AUC24 for the compound of Formula (I) are shown in Table 29 below. These PK parameters are consistent with observations from Phase 1 studies in healthy volunteers.

**Table 29. Cohort 1 Mean PK parameters of $T_{max}$, $C_{max}$, and $AUC_{24}$**

| | Day 1 | | | Day 14 | | |
|---|---|---|---|---|---|---|
| | $T_{max}$ | $C_{max}$ | $AUC_{24}$ | $T_{max}$ | $C_{max}$ | $AUC_{24}$ |
| **Mean** | **5.4** | **1305** | **10,292** | **4.4** | **1349** | **14,297** |
| **CV%** | 30 | 25 | 24 | 32 | 15 | 24 |

**[0503]** Additional measurements of cohort 1 and cohort 2 mean PK parameters of $T_{max}$, $C_{max}$, and $AUC_{24}$ for the compound of Formula (I) on Day 1 of dosing are shown in Table 30 below.

**Table 30: Mean PK parameters of $T_{max}$, $C_{max}$, and $AUC_{24}$ on Day 1 of dosing**

| | Cohort 1 50 mg- Ensure | | | Cohort 2 100 mg-Ensure | | |
|---|---|---|---|---|---|---|
| **Day 1** | **$T_{max}$* (h)** | **$C_{max}$ (ng/ml)** | **$AUC_{24}$ (h*ng/ml)** | **$T_{max}$ (h)** | **$C_{max}$ (ng/ml)** | **$AUC_{24}$ (h*ng/ml)** |
| **G.Mean** | 6 | 1,270 | 10,411 | 4 | 2,370 | 24,725 |
| **CV%** | - | 25 | 24 | - | 21 | 42 |
| **N** | 8 | 8 | 8 | 8 | 4 | 4 |
| *Median | | | | | | |

**[0504]** Additional measurements of cohort 1, cohort 2 and cohort 3 mean PK parameters of $T_{max}$, $C_{max}$, and AUC24 for the compound of Formula (I) on Day 14 of dosing are shown in Table 31 below.

**Table 31: Mean PK parameters of $T_{max}$, $C_{max}$, and AUC24 on Day 14 of dosing**

| | Cohort 1 50 mg- Ensure | | | Cohort 2 100 mg-Ensure | | | Cohort 3 100 mg w/evening Meal | | |
|---|---|---|---|---|---|---|---|---|---|
| Day 14 | Tmax* (h) | Cmax (ng/ml) | AUC24 (h*ng/ml) | Tmax (h) | Cmax (ng/ml) | AUC24 (h*ng/ml) | Tmax (h) | Cmax (ng/ml) | AUC24 (h*ng/ml) |
| G. Mean | 4 | 1,335 | 14,070 | 4 | 3,379 | 35,416 | 3 | 3,650 | 34,706 |

(continued)

| | Cohort 1 50 mg- Ensure | | | Cohort 2 100 mg-Ensure | | | Cohort 3 100 mg w/evening Meal | | |
|---|---|---|---|---|---|---|---|---|---|
| Day 14 | Tmax* (h) | Cmax (ng/ml) | AUC24 (h*ng/ml) | Tmax (h) | Cmax (ng/ml) | AUC24 (h*ng/ml) | Tmax (h) | Cmax (ng/ml) | AUC24 (h*ng/ml) |
| CV% | | 15 | 24 | | 31 | 7 | | 2 | 15 |
| N | 8 | 8 | 8 | 6 | 6 | 6 | 8 | 8 | 8 |
| *Median | | | | | | | | | |

**[0505]** Arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, day 1, and day 14. The androstenedione concentration profile on Day 1 and Day 14 shows a clear reduction from the baseline mean profile.

**[0506]** When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of ACTH show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 14A). Arithmetic mean values across all three timepoints show >=50% reductions from baseline at Day 1 and Day 14 (FIG. 14B).

**[0507]** When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of 17-OHP show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 15A). Arithmetic mean values across all three timepoints show >=40% reductions from baseline at Day 1 and Day 14 (FIG 15B).

**[0508]** When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of androstenedione show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 16A). Arithmetic mean values across all three timepoints show >=30% reductions from baseline at Day 1 and Day 14 (FIG. 16B).

**[0509]** A summary of reduction in 17-OHP and androstenedione in cohort 1 is shown in Table 32. Further, the androstenedione levels of three subjects was normalized by the treatment for the three subjects with Subject ID Nos. 001, 002, and 006).

**Table 32. Cohort 1 Summary of Reduction in 17-OHP and Androstenedione at each timepoint in the morning window (6 a.m. to 10 a.m.)**

| Subject ID | Sex/Age | Dosing Day | 17-OHP % change from baseline | | | Androstenedione % change from baseline | | |
|---|---|---|---|---|---|---|---|---|
| | | | 6 AM | 8 AM | 10 AM | 6 AM | 8 AM | 10 AM |
| **001** | F/37 | D1<br>D14 | -61.4<br>-90.3 | 14.7<br>-67.2 | -24.1<br>-37.2 | -42.0<br>-84.6 | 2.0<br>-58.6 | -19.5<br>-55.1 |
| **002** | F/25 | D1<br>D14 | -96.0<br>-37.7 | -95.5<br>-58.6 | 45.4<br>-24.9 | -68.0<br>-34.2 | -66.7<br>-47.8 | -21.7<br>-38.7 |
| **003** | M/49 | D1<br>D14 | -11.8<br>-24.5 | -46.6<br>-5.2 | -34.0<br>-22.9 | -13.4<br>-7.5 | -47.1<br>-10.8 | -22.7<br>-16.0 |
| **004** | M/36 | D1<br>D14 | -13.7<br>-53.6 | 17.1<br>-46.8 | 10.1<br>-35.8 | 4.5<br>-13.8 | 15.9<br>-15.2 | 3.0<br>-21.2 |
| **005** | F/27 | D1<br>D14 | -24.4<br>-78.8 | -83.6<br>-95.1 | -52.2<br>-86.3 | -35.6<br>26.7 | -50.3<br>-13.7 | -33.5<br>-10.9 |
| **006** | M/19 | D1D14<br>D14 | -5.1<br>-25.4 | -1.1<br>-20.4 | -97.8<br>-98.3 | -10.0<br>-67.8 | -18.5<br>-62.7 | -78.9<br>-92.1 |
| **007** | M/25 | D1<br>D14 | -50.0<br>14.9 | -28.0<br>4.0 | -27.4<br>-7.1 | -24.8<br>-4.8 | -30.0<br>-36.8 | -15.8<br>-30.2 |
| **008** | F/31 | D1<br>D14 | -64.5<br>-59.0 | -80.7<br>-65.2 | -92.8<br>-89.1 | -12.2<br>74.5 | 7.0<br>99.4 | -9.3<br>59.2 |

**Table 33. Cohort 1 Summary of PK parameters of $T_{max}$, $C_{max}$, and $AUC_{24}$ for each subject at days 1 and 14**

| Day 1 | Day 1 | | | Day 14 | | |
|---|---|---|---|---|---|---|
| **Subject ID** | **$T_{max}$ (h)** | **$AUC_{24}$ $C_{max}$ (ng/ml) (h*ng/ml)** | | **$T_{max}$ (h)** | **$C_{max}$ (ng/ml)** | **$AUC_{24}$ (h*ng/ml)** |
| **001** | 6 | 1830 | 14,487 | 6 | 1570 | 20,863 |
| **002** | 6 | 1210 | 11,829 | 4 | 1610 | 15,494 |
| **003** | 6 | 1060 | 11,068 | 3 | 1310 | 15,599 |
| **004** | 4 | 1670 | 9,669 | 3 | 1160 | 10,180 |
| **005** | 8 | 961 | 9,266 | 6 | 1550 | 15,130 |
| **006** | 4 | 1030 | 6,574 | 3 | 1090 | 10,288 |
| **007** | 6 | 1550 | 8,239 | 6 | 1170 | 12,880 |
| **008** | 3 | 1130 | 11,209 | 4 | 1330 | 13,944 |
| **Mean** | **5.4** | **1305** | **10,292** | **4.4** | **1349** | **14,297** |
| **CV%** | 30 | 25 | 24 | 32 | 15 | 24 |
| **N** | 8 | 8 | 8 | 8 | 8 | 8 |

**[0510]** After 14 days of once-daily compound of Formula (I) administration, a majority of participants in Cohorts 1-3 showed reduced serum concentrations of adrenal androgens and precursors. Mean changes from baseline (±standard deviation) in Cohort 1 were as follows: 17-OHP, -2341.0±1535.0 ng/dL; androstenedione, -98.4±98.7 ng/dL; and ACTH, -157.0±194.9 pg/mL. Mean reductions were larger in Cohort 2 (17~OHP, -4406.0±5516.1; androstenedione, -362.8±354.0; ACTH, -180.9±155.2) and Cohort 3 (17-OHP, -4760.1±4018.2; androstenedione, -210.9±188.6; ACTH, -358.9±177.6), suggesting a possible dose response. FIGs. 17A-17C, 18A-18C, and 19A-19C depict results from Cohorts 1, 2, and 3, respectively.

***Summary***

**[0511]** The results from this ongoing Phase II open-label study demonstrated a reduction of at least 50 percent from baseline in 17-hydroxyprogesterone (17-OHP) and adrenocorticotropic hormone (ACTH) levels in more than 50 percent of CAH patients in cohort 1 treated with the compound of Formula (I) for 14 days (i.e., 6 of 8 patients in cohort 1 had a reduction of ≥50% from baseline levels of 17-OHP during at least one morning window timepoint, see, e.g., Table 32). Meaningful reductions were also observed in other biomarkers, including androstenedione (i.e., 4 of these patients also had a reduction of ≥50% from baseline levels of androstenedione during at least one morning window timepoint, see, e.g., Table 32). The greater reductions in biomarkers in cohorts 2 and 3, treated with double the dose of the compound of Formula (I) compared with cohort 1, suggest a possible dose response. Further, the compound of Formula (I) was well-tolerated with a relatively small number of mild adverse events (AEs) reported (e.g., headache, ovulation pain, fatigue, localized infection (toe), dizziness, nausea, URI, contusion with the most common being headache). No clinically significant findings from routine labs, vital signs, or electrocardiograms were found.

**Example 9: Reference Formulation 1 of the compound of Formula (I)**

**[0512]** Tables 34A and 34B show Reference formulation 1 of the compound of Formula (I) as used in the clinical studies described in Examples 6 and 8, above. An example manufacturing process is shown in FIG. 20. Another example manufacturing process is shown in FIG. 21.

Table 34A:

| Component | Quality Standard | Function | 50 mg Capsule | |
|---|---|---|---|---|
| | | | Weight mg/unit) | % (w/w) |
| Compound of Formula (I), free base | In-house | Active Ingredient | 50.0 | 10.0 |
| Medium-Chain Triglycerides Labrafac TM Lipophile WL1349) | NF | Oily Phase Vehicle | 196.0 | 39.2 |
| Propylene Glycol Dicaprylate/Dicaprate, (LabrafacTM PG) | NF | Emulsifying Agent | 102.0 | 20.4 |
| Lauroyl Polyoxyl-32 Glycerides (Gelucire® 44/14) | NF | Nonionic Surfactant & Solubilizing Agent | 95.0 | 19.0 |
| Vitamin E Polyethylene Glycol Succinate (Kolliphor® TPGS) | USP/NF | Solubilizing Agent | 57.0 | 11.4 |
| **Total Emulsion Weight** | | | **500.0** | **100.0** |
| Gelatin Capsule Shell. Size #00, Swedish Orange cap/body; (Coni-Snap®) | Non-Pharmacopoeial | Capsule Shell | -- | |
| Gelatin Powder, 220 Bloom | USP | Capsule shell banding agent | -- | -- |
| Purified Water | USP | Capsule shell banding solvent | -- | -- |

Table 34B:

| Component | Quality Standard | Function | 50 mg Capsule | |
|---|---|---|---|---|
| | | | Weight (mg/un it) | % (w/w) |
| Compound of Formula (I), free base | In-house | Active Ingredient | 50.0 | 10.0 |
| Medium-Chain Triglycerides (caprylic:capric acid 60: 40; Miglyol 812N) | Ph. Eur./NF | Vehicle | 195.85 | 39.2 |
| Propylene Glycol Dicaprylocaprate, (LabrafacTM PG) | Ph. Eur. | Vehicle | 102.15 | 20.4 |
| Lauroyl macrogolglycerides type 1500-Lauroyl polyoxylglycerides type 1500 (Gelucire® 44/14) | Ph. Eur./NF | Surfactant | 95.0 | 19.0 |
| Vitamin E Polyethylene Glycol Succinate, 260 mg/g d-alpha tocopherol (Vitamin E/TPGS 260) | NF | Surfactant | 57.0 | 11.4 |
| **Total Emulsion Weight** | | | **500.0** | **100.0** |
| Orange opaque hard capsule, size 0, composed of gelatin, titanium dioxide and red ferric oxide (Swedish Orange ®) | Non Pharmacopoeial | Capsule Shell | -- | -- |
| Ethanol (96%) and Purified Water | USP | Capsule shell banding solvent | -- | -- |

**Example 10: Study Evaluating Effect of Ensure Plus, Ensure Pudding, Milk and High Fat Meal on Reference Capsule**

**Study design**

**[0513]** This is a Phase 1, open-label, randomized, four-period crossover study to evaluate the effect of food with different levels of fat and caloric content on the PK, safety, and tolerability of the compound of Formula (I) in healthy adult subjects.

**[0514]** A total of 16 healthy adult subjects (8 males and 8 females) will be randomly assigned to 1 of 4 treatment sequences (4 subjects per sequence [2 males and 2 females per sequence]; see Table 35 below). During each treatment period, subjects will receive a single dose of the compound of Formula (I) 100 mg administered with the appropriate meal, according to the randomization scheme. There will be a washout of at least 21 days between each dose.

**Table 35:**

| Treatment Sequence | Treatment Period 1 | Treatment Period 2 | Treatment Period 3 | Treatment Period 4 |
|---|---|---|---|---|
| 1 | Reference meal | Test meal 1 | Test meal 2 | Test meal 3 |
| 2 | Test meal 1 | Test meal 3 | Reference meal | Test meal 2 |
| 3 | Test meal 2 | Reference meal | Test meal 3 | Test meal 1 |
| 4 | Test meal 3 | Test meal 2 | Test meal 1 | Reference meal |
| Reference meal: vanilla-flavored Ensure Plus® Test meal 1: Low fat, low caloric content meal 1 Test meal 2: Low fat, low caloric content meal 2<br>Test meal 3: standard high fat, high caloric content meal | | | | |

**[0515]** After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days before Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1 and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During each treatment period, subjects will fast overnight for at least 10 hours until the start of the assigned meal, according to the randomization scheme, and ingest the study drug at approximately 0800 hours. Subjects must complete the entire meal within the specified time period and should not consume any other food for 4 hours after dosing. For all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water provided with study drug dosing and planned meals.

**[0516]** On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 100 mg. Blood samples will be collected for PK analysis over a period of 36 hours during the in-house stay. During each treatment period, subjects will remain in the clinic on the day of dosing and will be discharged on Day 2 after completing all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects will return for an outpatient visit to the clinic for PK blood sample collection and safety assessments. On Day 21 of treatment periods 1 to 3, subjects will arrive at the site and have Day 21 assessments completed and they will stay overnight at the site and begin Day 1 of the subsequent treatment period the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 4 (21 ± 2 days after treatment period 4 dosing) or upon early termination.

**[0517]** Blood samples for PK d/conducted at scheduled times throughout the study.

**Study population**

**[0518]** Sixteen healthy adult subjects (8 males and 8 females) between 18 and 55 years of age, inclusive, who meet all protocol eligibility criteria, will be enrolled.

**Duration of treatment**

**[0519]** The expected duration of study participation for each healthy adult subject will be approximately 16 weeks, including up to 28 days of screening, 4 days of dosing with at least 21 days between consecutive doses, and a final follow-up study visit 21 days (± 2 days) after receiving the last dose of study drug during treatment period 4.

**Test product, dose, and mode of administration**

**[0520]** The compound of Formula (I) will be supplied as capsules for oral administration (encapsulated, lipidic semi-solid formulation, e.g., Example 9). The compound of Formula (I) capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. During each treatment period, subjects will receive two 50 mg capsules (100 mg) of the study drug along with a meal and water as defined by the randomization scheme. The food, water, and study drug administration are as follows:

Reference meal: Two capsules of study drug will be administered approximately 5 minutes after the start of a liquid dietary supplement (i.e., Ensure Plus® [237 mL container]) and an additional 120 mL of water for study drug dosing.
Test meal 1: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 1 with 120 mL of water for study drug dosing.
Test meal 2: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 2 with 120 mL of water for study drug dosing.
Test meal 3: Two capsules of study drug will be administered approximately 30 minutes after the start of a high fat, high caloric meal with 120 mL of water for study drug dosing.

**CRITERIA FOR EVALUATION**

**Pharmacokinetics**

**[0521]** Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

**[0522]** The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-}tlast}$)
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration ($C_{max}$)
- Time to achieve maximum plasma concentration ($t_{max}$)
- Delay time between time of dosing and time of appearance of measurable test article ($T_{lag}$)
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant ($\lambda z$)
- Apparent mean residence time (MRT)
- Molar AUC ratio of primary metabolite(s) to the parent drug compound of Formula (I). The following plasma PK parameters will be calculated only for the compound of Formula (I):
- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

**Safety Assessments**

**[0523]** Safety will be monitored throughout the study and will include the following assessments:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiograms (ECGs)

**Statistical methods**

**[0524]** Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by meal type (test meal/reference meal) using descriptive statistics. Two-sided 90% confidence intervals will be calculated for the ratio of each test meal versus the reference meal for $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tlast}$, and $C_{max}$ for the compound of Formula (I)

and metabolites.

**[0525]** Safety data will be summarized with descriptive statistics.

**Results**

***Pharmacokinetic results***

**[0526]** Pharmacokinetic results are shown in Table 36 below.

**Table 36: Summary of Plasma Pharmacokinetic Parameters**

| | | Compound of Formula (I) Plasma Concentration | | | |
|---|---|---|---|---|---|
| **Parameter (units) Statistic** | **Ensure Plus (Fed) (N=18)** | **Ensure Pudding (Fed) (N=18)** | **Whole Milk (Fed) (N=17)** | **High Fat Meal (Fed) (N=17)** | |
| **$AUC_{0\text{-tlast}}$ (ng×hr/mL)** | | | | | |
| Mean (SD) | 36703 (17400) | 34077 (11597) | 35561 (15866) | 55487 (23242) | |
| Geom CV(%) | 58 | 39.7 | 44.6 | 41.9 | |
| **$AUC_{0\text{-}\infty}$ (ng×hr/mL)** | | | | | |
| | Mean | 45386 (19648) | 40037 (9515) | 46737 (17395) | 63755 (19139) |
| | Geom CV(%) | 43.3 | 23.8 | 38.8 | 31 |
| **$C_{max}$ (ng/mL)** | | | | | |
| | Mean (SD) | 3090 (1070) | 3038 (984) | 2835 (1005) | 4336 (1938) |
| | Geom CV(%) | 39.7 | 34.9 | 34.5 | 53.6 |
| **$t_{max}$ (hr)** | | | | | |
| | Median (min, max) | 5.0 (2.0, 10.0) | 5.0 (4.0, 6.0) | 5.0 (4.0, 7.0) | 5.0 (4.0, 7.0) |
| **$T_{lag}$ (hr)** | | | | | |
| | Mean (SD) | 0.38 (0.46) | 0.20 (0.25) | 0.16 (0.31) | 0.29 (0.37) |
| **$t_{½}$ (hr)** | | | | | |
| | Mean (SD) | 361 (263) | 373 (196) | 373 (143) | 326 (120) |
| | Geom CV(%) | 61.1 | 48.6 | 37.1 | 33.8 |
| **CL/F (L/hr)** | | | | | |
| | Mean (SD) | 2.49 (0.956) | 2.636 (0.659) | 2.427 (0.975) | 1.706 (0.526) |
| | Geom CV(%) | 41.2 | 24.8 | 38.8 | 31.1 |
| **Vz/F (L)** | | | | | |
| | Mean (SD) | 1254 (906) | 1414 (720) | 1308 (627) | 816 (378) |
| | Geom CV(%) | 72.7 | 58.4 | 61.3 | 54.9 |

**Example 11: Spray-dried Dispersion Granule Formulation of the Compound of Formula (I) (SDD-G)**

**[0527]** Table 37 shows a granule formulation of the compound of Formula (I) using a SDD prepared according to Example 3, above. An example manufacturing process is shown in FIG. 22A and FIG. 22B.

**Table 37:**

| Component | Quality Standard | Function | 50 mg Sachet | | Batch Weight (g) |
|---|---|---|---|---|---|
| | | | Weight (mg/ unit) | % (w/w) | |
| Example 3, SDD | In-house | Drug Substance | 200.0 | 13.33 | 40 |
| Calcium Silicate (ZEOPHARM 250) | NF | Glidant | 10.0 | 0.67 | 2 |
| Mannitol (Pearlitol 200SD) | NF / EP / JP | Filler | 832.5 | 55.5 | 166.5 |
| Microcrystalline Cellulose (Avicel PH-102) | NF / EP / JP | Filler | 300.0 | 20.0 | 60 |
| Croscarmellose Sodium (Ac-Di-Sol®) SD711 | NF / EP / JP | Disintegrant | 150.0 | 10.0 | 30 |
| Sodium Stearyl Fumarate | NF / EP / JP | Lubricant | 7.5 | 0.5 | 1.5 |
| Total | | | 1500 | 100.0 | 300 |

**Example 12: Liquid Formulation 1 of the Compound of Formula (I)**

**[0528]** Table 38 shows liquid formulation 1 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 23.

**Table 38:**

| Component | Quality Standard | Function | 50 mg/mL Oral Solution | | Batch Weight (g) |
|---|---|---|---|---|---|
| | | | Weight (mg/mL) | % (w/v) | |
| Compound of Formula (I) FB | In-house | Drug Substance | 50.0 | 5 | 20.03 |
| Saccharin | NF / EP | Sweetener | 1.5 | 0.15 | 0.61 |
| Butylated hydroxytoluene | NF / EP | Anti-oxidant | 1.7 | 0.17 | 0.69 |
| FONA orange flavor | NF | Flavor | 1.0 | 0.1 | 0.41 |
| Labrafac Lipophile WL1349 | NF / EP | Liquid Vehicle | to 1 mL | 94.58 | 358.87 |
| Total | | | 1 mL | 100.0 | 380.6 |

**Example 13: Liquid Formulation 2 of the Compound of Formula (I)**

**[0529]** Table 39 shows liquid formulation 2 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 24.

**Table 39:**

| Component | Quality Standard | Function | 50 mg/mL Oral Solution | | Batch Weight (g) |
|---|---|---|---|---|---|
| | | | Weight (mg/mL) | % (w/v) | |
| Compound of Formula (I) FB | In-house | Drug Substance | 50.0 | 5 | 20.17 |
| Saccharin | NF / EP | Sweetener | 1.5 | 0.15 | 0.61 |

(continued)

| Component | Quality Standard | Function | 50 mg/mL Oral Solution | | Batch Weight (g) |
|---|---|---|---|---|---|
| | | | Weight (mg/mL) | % (w/v) | |
| Butylated hydroxytoluene | NF / EP | Anti-oxidant | 1.7 | 0.17 | 0.68 |
| LABRAFIL M 1944 CS | NF / EP | Surfactant | 200.0 | 20 | 80.16 |
| FONA orange flavor | NF | Flavor | 1.0 | 0.1 | 0.40 |
| Labrafac Lipophile WL1349 | NF / EP | Liquid Vehicle | to 1 mL | 74.58 | 278.68 |
| Total | | | 1 mL | 100.0 | 380.7 |

**Example 14: A Phase I, Open-Label Study to Evaluate the Pharmacokinetics, Relative Bioavailability, Effect of Food, Safety and Tolerability of Different Compound of Formula (I) Prototype Formulations in Healthy Adult Subjects.**

**Methodology**

**[0530]** This is a single center, open-label, randomized, single dose 4-period crossover study in healthy adult subjects designed to investigate the pharmacokinetic (PK) and safety of up to 4 compound of Formula (I) liquid lipidic prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulations, 50 mg/mL), a compound of Formula (I) spray dried dispersion formulation (compound of Formula (I) Granule for Sprinkle, 25 - 50 mg) and compound of Formula (I), 50 mg Capsules (Reference). It is planned to enroll 36 subjects to be allocated as 3 cohorts of 12 subjects per cohort, with 6 sub-cohorts of 6 subjects per sub-cohort. In each of these 6 sub- cohorts, 6 subjects will be assigned to one of 3 sub-cohorts where a single oral dose of Investigational Medicinal Product (IMP) is administered in 4 dosing periods (Periods 1 to 4) in multiple fed or fasted states or to one of 3 sub-cohorts where a single oral dose of IMP is administered in 2 dosing periods (Periods 1 and 2) only in the fed state. Within each sub-cohort, subjects will also be randomized before administration of the first dose of IMP in Period 1 to one of the following treatment sequences (Table 40):

**Table 40:**

| Sub-Cohort | Sequence | Number of Subjects | Total Number of Periods Dosed | Regimen | | | |
|---|---|---|---|---|---|---|---|
| | | | | Period 1 | Period 2 | Period 3 | Period 4 |
| 1A | ABEF | 3 | 4 | Regimen A | Regimen B | Regimen E | Regimen F |
| | BAEF | 3 | 4 | Regimen B | Regimen A | Regimen E | Regimen F |
| 1B | AB | 3 | 2 | Regimen A | Regimen B | N/A | N/A |
| | BA | 3 | 2 | Regimen B | Regimen A | N/A | N/A |
| 2A | ADEF | 3 | 4 | Regimen A | Regimen D | Regimen E | Regimen F |
| | DAEF | 3 | 4 | Regimen D | Regimen A | Regimen E | Regimen F |
| 2B | AD | 3 | 2 | Regimen A | Regimen D | N/A | N/A |
| | DA | 3 | 2 | Regimen D | Regimen A | N/A | N/A |

(continued)

| Sub-Cohort | Sequence | Number of Subjects | Total Number of Periods Dosed | Regimen | | | |
|---|---|---|---|---|---|---|---|
| | | | | Period 1 | Period 2 | Period 3 | Period 4 |
| 3A | ACEF | 3 | 4 | Regimen A | Regimen C | Regimen E | Regimen F |
| | CAEF | 3 | 4 | Regimen C | Regimen A | Regimen E | Regimen F |
| 3B | AC | 3 | 2 | Regimen A | Regimen C | N/A | N/A |
| | CA | 3 | 2 | Regimen C | Regimen A | N/A | N/A |

**[0531]** At informed consent, subjects will agree either to participate in 2 study periods or 4 study periods. Once placed into a sub-cohort, the order in which subjects receive the study treatments will be randomized based on the schedule above.

**[0532]** Subjects will receive up to 4 regimens in up to 4 periods in an order according to the randomization schedule within each sub-cohort.

**[0533]** The effect of different prandial states on the PK of the compound of Formula (I) may be explored in Periods 3 and 4 by administering in the fasted state or after an alternative meal (e.g. high fat, standard or light breakfast, etc.).

**[0534]** The proposed regimens are presented in Table 41 below:

**Table 41:**

| Regimen | Investigational Medicinal Product | Dose | Route of Administration | Prandial State |
|---|---|---|---|---|
| A | Compound of Formula (I), 50 mg Capsules (Reference) | 50 mg | Oral | Fed (Ensure Plus) |
| B | Compound of Formula (I) Oral Solution, Prototype Formulation 1,50 mg/mL | 50 mg | Oral | Fed (Ensure Plus) |
| C | Compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL | 50 mg | Oral | Fed (Ensure Plus) |
| D | Compound of Formula (I) Granule for Sprinkle, 25 - 50 mg | 50 mg | Oral | Fed (Ensure Plus) |
| E | Compound of Formula (I) Oral Solution, Prototype Formulation 1 | 100 mg | Oral | Fed (Ensure Plus) |
| F | Compound of Formula (I) Oral Solution, Granule for Sprinkle | 50 mg | Oral | Fed (alternative meal) |

**Study Design:**

**[0535]** Subjects will be screened for eligibility to participate in the study up to 28 days before the first dose of IMP in Period 1. Each study period will follow the same study design. Subjects will be admitted to the clinical unit on the evening prior to IMP administration (Day -1). For Periods 1 and 2 (Regimen A and one of either Regimens B, C or D), all subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement (Ensure Plus). For Periods 3 and 4 (Regimens E and F), subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement or an alternate prandial state (fasted or alternative meal). IMP administration will be performed on Day 1 with an appropriate interval between subjects based on logistical requirements (approximately 10 min). Meals will be standardized for each treatment regimen across periods.

**[0536]** Subjects will remain in the clinical unit until 36 h post-dose when they will be discharged. Subjects will return to the clinical unit at 168 h (7 days) and 336 h (14 days) postdose for a PK blood sample and safety assessments. The

minimum washout between IMP dosing occasions will be 14 days between Periods 1 and 2 and 21 days or more to accommodate interim data reviews between Periods 2 and 3 and between Periods 3 and 4.

**[0537]** There will be a follow-up phone call 18 to 24 days post-final visit to ensure the ongoing wellbeing of subjects.

**[0538]** Following the completion of Period 2 for all cohorts, there will be an interim data review during which the PK and safety data will be reviewed, plus any relevant emerging Chemistry, Manufacturing and Control (CMC) stability study information, to determine the formulation, dose level and prandial state in which to administer the IMP in Period 3 (Regimen E). There will be a similar interim review following completion of Period 3 (administration of Regimen E) to determine the formulation, dose level and prandial state in which to administer the IMP in Period 4 (Regimen F). The criteria for the interim decisions will be based on available compound of Formula (I) PK data: e.g., $C_{max}$, $T_{max}$, AUC(0-36), $F_{rel}$ and safety data.

**Number of Subjects Planned:**

**[0539]** It is planned to enroll 36 healthy male and female (non-pregnant, non-lactating) subjects in 6 sub-cohorts of 6 subjects per sub-cohort. These sub-cohorts will be combined in sets of 2 to create 3 cohorts of n = 12 for Periods 1 and 2 to target data in 10 evaluable subjects in each cohort for the primary objectives per formulation variant. A total of 18 subjects, 6 from each of Sub-Cohorts 1A, 2A and 3A participating in Periods 1 and 2, will additionally participate in Periods 3 and 4 with a target of a minimum of 6 evaluable subjects. A subject will be considered evaluable for a particular regimen if they have received an IMP and has completed sufficient planned PK assessments up to 336 h (14 days) after dosing for that regimen to allow for the assessment of study endpoints. A subject will be considered evaluable for a particular comparison (e.g., food effect, relative bioavailability) if they have received both IMPs under comparison and have sufficient PK data up to 14 days after each regimen to allow for assessment of study endpoints.

**[0540]** Subjects withdrawn due to an IMP-related adverse event (AE) will not be replaced. Subjects who are withdrawn for other reasons may be replaced as required by agreement between the principal investigator (PI) and sponsor to ensure sufficient numbers of evaluable subjects at the end of each study period. Replacement subjects may be required to be dosed with specific formulations from the previous regimens in order to obtain the minimum number of evaluable subjects required for interim decisions and to obtain data in any other regimen that is required to fulfil the study objective comparisons, with the exception that any previously dosed IMP that has been considered sub-optimal will not be dosed. Up to 8 replacement subjects in total may be enrolled into the study. The maximum number of subjects that may be dosed is 44 in total.

**[0541]** If a subject withdraws from Sub-Cohort 1A, 2A or 3A after Period 2, it is acceptable to replace them with a subject from Sub-Cohort 1B, 2B or 3B provided the subject signs an updated consent form agreeing to participate in four treatment periods. At the discretion of the investigator, such a subject may not be required to undergo repeat screening procedures.

**Duration of Study:**

**[0542]** For subjects enrolled to receive single dose administration on 4 separate occasions in Periods 1 to 4 (Sub-Cohorts 1A, 2A and 3A), the estimated time from screening until the follow-up phone call is approximately 15 to 16 weeks.

**[0543]** For subjects enrolled to receive single dose administration on 2 separate occasions in Periods 1 to 2 only (Sub-Cohorts 1B, 2B and 3B), the estimated time from screening until the follow-up phone call is approximately 8 to 9 weeks.

**Pharmacokinetic Assessments:**

**[0544]** The plasma concentration data for a compound of Formula (I) will be analyzed for final reporting by Quotient Sciences and for interim reviews by Neurocrine Biosciences, Inc. (NBI), using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA). NBI will be responsible for PK analysis for interim review.

**[0545]** PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the following PK parameters (Table 42) where possible and appropriate:

**Table 42:**

| | |
|---|---|
| $T_{lag}$ | Time prior to the first measurable (nonzero) concentration |
| $T_{max}$ | Time to maximum plasma concentration |
| $C_{max}$ | Maximum plasma concentration |
| $AUC_{0\text{-}tlast}$ | Area under the plasma concentration versus time curve (AUC) from 0 h to last measurable concentration |

(continued)

| | |
|---|---|
| $AUC_{0\text{-}inf}$ | AUC from 0 h extrapolated to infinity |
| $AUC_{extrap}$ | Percentage of $AUC_{0\text{-}inf}$ extrapolated beyond the last measurable concentration |
| Lambda-z | Slope of the apparent terminal phase |
| $T_{1/2}$ | Apparent terminal half-life |
| CL/F[a] | Apparent systemic clearance after oral administration |
| Vd/F[a] | Apparent volume of distribution based on the area after a single oral administration |
| MRT | Mean residence time |
| MPR $AUC_{0\text{-}tlast}$ | Metabolite to parent ratio based on $AUC_{0\text{-}tlast}$ |
| MPR $AUC_{0\text{-}inf}$ | Metabolite to parent ratio based on $AUC_{0\text{-}inf}$ |

**Taste Assessments:**

**[0546]** Taste will be assessed for each IMP formulation and vehicle (e.g., Ensure Plus, soft food) using a questionnaire designed for this purpose and adapted for this specific study as required.

**[0547]** The questionnaire will ask subjects to rate the acceptability of smell, sweetness, bitterness, flavor, mouth feel, and aftertaste on a 6-point scale, and overall experience on a 5-point scale for each IMP formulation independently of any previous formulations.

**Statistical Methodology:**

**[0548]** Descriptive summaries for all safety data, PK assessments and taste questionnaire data will be provided. No hypothesis testing will be performed for the safety or taste questionnaire data.

**Periods 1 and 2 - for Each Cohort Separately**

***Relative Bioavailability***

**[0549]** Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability (Frel) using a mixed effects model with terms for regimen, period and sequence as fixed effects and subject within sequence as a random effect. Ratios of geometric means (GMRs) and 90% confidence interval (CI) for the relevant comparison of interest, i.e., between each of the prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulation 1, 50 mg/mL, e.g., Example 12; compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL, e.g., Example 13; and compound of Formula (I) Granule for Sprinkle, 25 - 50 mg, e.g. Example 11 [Regimens B, C and D, respectively]) and compound of Formula (I), 50 mg Capsules, e.g., Example 9 (Reference; Regimen A) will be presented.

**All Periods (Periods 1 to 4)**

*Food Effect*

**[0550]** Statistical modelling will be performed on the compound of Formula (I) PK parameters AUC(0-tlast), AUC(0-inf) and Cmax to assess for the effects of food, if relevant. The natural log-transformed PK parameters will be analyzed for bioavailability using a mixed effects model with terms for prandial state (and meal type if applicable) as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparisons of interest will be presented where the ratio is defined as fasted/fed or test meal/reference meal (if applicable).

***Relative Bioavailability***

**[0551]** Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability using a mixed effects model with terms for regimen as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparison of interest i.e., between each of the prototype formulations (Regimens E and F, IMPs to be determined by interim reviews

following completion of Periods 2 and 3) and compound of Formula (I), 50 mg Capsules (Reference; Regimen A) will be presented.

**Results**

**[0552]** Preliminary PK data is summarized in Table 43 below:

**Table 43: Preliminary Data from Periods 1 and 2**

| | A- Reference | B-Oral Solution 1 | C-Oral Solution 2 | D- SDD Granule |
|---|---|---|---|---|
| N | 35 | 12 | 12 | 12 |
| Tmax * (h) | 5<br>(2,6) | 6<br>(5,7) | 5<br>(5,7) | 5<br>(5,7) |
| Cmax (ng/ml) | 1361<br>(33) | 790<br>(31) | 1082<br>(46) | 1075<br>(35) |
| AUC36 (h*ng/ml) | 9452<br>(30) | 5556<br>(34) | 7582<br>(37) | 6691<br>(41) |
| *Geometric Mean /CV% for AUC and Cmax; Median for Tmax | | | | |

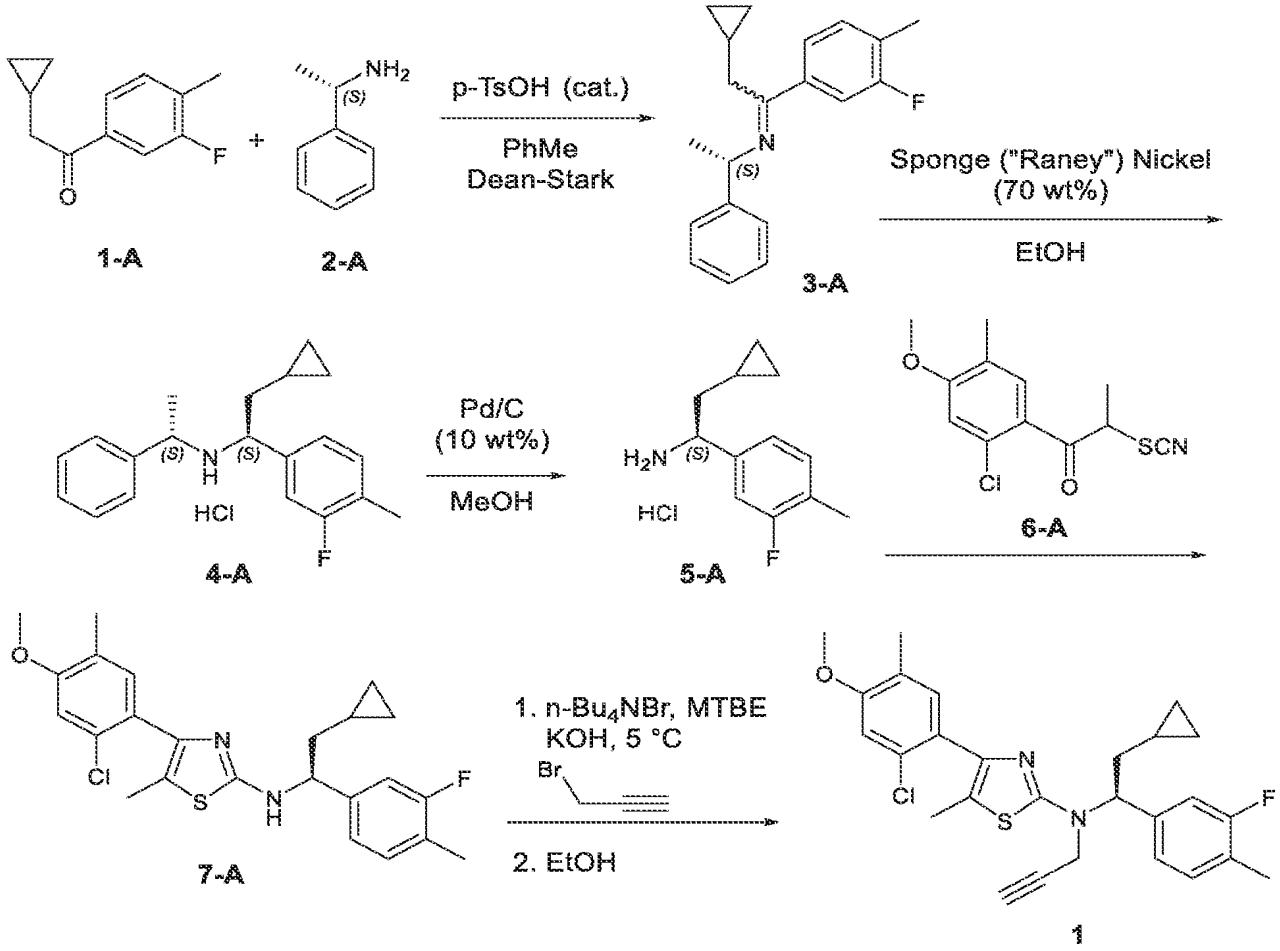
**Example 15. Compound of Formula (I) Crystalline Free Base Form I**

**Example 15A**

**Scheme 1: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), Form I)**

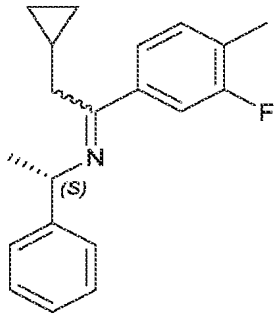
**[0553]**

Scheme 1




Step 1: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-(1-phenylethyl)ethan-1-imine (Compound 3-A)

**[0554]**



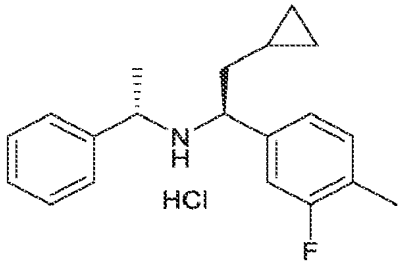
Compound 3-A

**[0555]** A mixture of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (1-A, 150.7 kg, 1 eq., as a 27.6% w/w solution in toluene, Example 15C), (*S*)-(-)-1-Phenylethylamine (2-A, 112.9 kg, 1.19 eq.), and *p*-toluenesulfonic acid (7.4 kg, 0.05 eq.) is refluxed at 110 - 120 °C for 23 - 25 h in a reactor set up in a Dean-Stark configuration. The solvent is then removed at 125 - 135 °C under atmospheric pressure until distillation halts and a portion of toluene (275 kg, 2.24 w/w) is added to afford a suspension. The suspension is refluxed at 110 - 120 °C for 23 - 25 h. The mixture is cooled to

22 °C and washed twice with aqueous $NH_4Cl$ (10%, 301.2 kg, 0.72 eq.) and once with aqueous $NaHCO_3$ (5%, 301.2 kg, 0.23 eq., check pH 8 - 9). The solvent is removed at 125 - 135 °C and atmospheric pressure to a target volume of 256 L, the mixture is filtered over celite, the cake is washed with toluene (25 kg). The resulting mixture containing compound 3-A is used directly in the next step without isolation. The yield is determined by correcting for the LOD and GC-FID purity of the sample (208.4 kg, 90.0% corrected, 0.89% Compound 2-A). EI-MS: 294.1 $[M\sim H]^+$, 190.1 $[M-C_6H_5CH(CH_3)]^+$, 105.1 $[C_6H_5CH(CH_3)]^+$.

Step 2: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-((*S*)-1-phenylethyl)ethan-1-amine hydrochloride (Compound 4-A)

**[0556]**



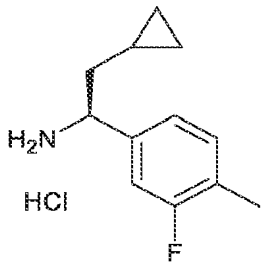

Compound 4-A

**[0557]** Sponge nickel catalyst (144 kg, 0.70 w/w, shipped as a 50% w/w suspension in water) is added to a hydrogenation reactor, equipped with a dip tube capable of removing material from the top of the mass inside, minimizing the amount of water introduced. The supernatant is discarded, ethanol (329.3 kg, 1.58 w/w, anhydrous) is added, the suspension is stirred and then allowed to settle. This process is repeated four more times and the Karl Fisher (KF) of the supernatant is checked (≤ 1% $H_2O$ w/w). Compound 3-A (208.4 kg, 1 eq., as a 62.6% solution in toluene) is added to the mixture in the hydrogenation reactor and ethanol (387.6 kg, 1.86 w/w) is used to rinse the addition flask into the hydrogenation reactor. The hydrogenation reactor is pressurized/depressurized twice with nitrogen (2 bar) and twice with hydrogen (5 bar) then pressurized with hydrogen (9.8 - 10.2 bar) and heated to 33 - 37 °C and stirred for 17 - 19 h. The system is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed with three times with ethanol (493.8 kg, 2.37 w/w). HCl (concentrated, 83.4 kg, 1.07 eq.) is added and the mixture stirred 25 - 35 min at 20

**[0558]** - 24 °C. The mixture is concentrated by distillation at 78 - 80 °C and atmospheric pressure to remove water with a distillate target volume of 1167 L (5.6 L/kg, Compound 3-A) and the KF of the solution is checked (≤ 1.5% $H_2O$ w/w). The mixture is stirred at 48 - 52 °C for 55 - 65 min, then 68 - 72 °C for 55 - 65 min, then cooled to 20 - 24 °C at a rate of 12 °C/h and stirred for 25 - 35 min, then cooled to 0 - 4 °C at a rate of 10 °C/h and stirred for 55 - 65 min. The suspension is filtered, the cake is washed twice with precooled ethanol (329.2 kg, 1.58 w/w, 0 °C), and the collected solid is dried at 40 °C to afford compound 4-A (156.5 kg, 66.4% uncorrected). $^1H$ NMR (400 MHz, DMSO-*d*6) δ ppm -0.33 - -0.06 (m, 2 H) 0.11 - 0.31 (m, 3 H) 1.57 (d, *J*=6.57 Hz, 3 H) 1.95 (br t, *J*=7.07 Hz, 2 H) 2.26 (d, *J*=1.26 Hz, 3 H) 3.68 (br d, *J*=7.83 Hz, 1 H) 3.92 (br t, *J*=6.44 Hz, 1H) 6.98 (dd, *J*=7.71, 1.14 Hz, 1H) 7.28 - 7.36 (m, 2 H) 7.37 - 7.50 (m, 5 H). ESI-MS: 298.2 m/z $[M+H]^+$.

Step 3: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-amine hydrochloride (Compound 5-A)

**[0559]**

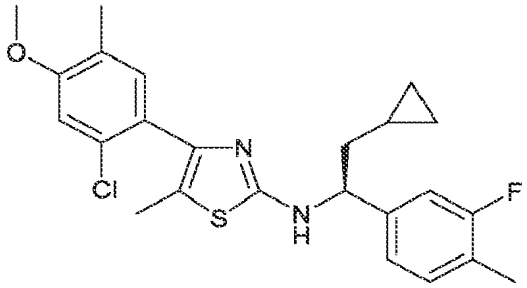



Compound 5-A

**[0560]** Compound 4-A (156.5 kg, 1.00 eq.) and Pd/C (7.8 kg, 10% Pd basis) are added to an inerted hydrogenation reactor. The reactor is then pressurized/depressurized twice with nitrogen (2 bar) and then methanol (494.5 kg, 3.16 w/w) is added. The reactor is depressurized/pressurized three times with nitrogen (2 bar) then three times with hydrogen (5 bar), pressurized with hydrogen (9.8 - 10.2 bar), heated to 58 - 62 °C and stirred for 7 - 9 h. The reaction mixture is cooled to 20 - 24 °C. The reactor is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed three times with methanol (492.9 kg, 3.15 w/w). The solution is concentrated at 63 - 67°C and atmospheric pressure to a distillate target volume of 1408 L (9.0 L/kg Compound 4-A). *n*-Heptane (1173.8 kg, 7.5 w/w) is added and the mixture is refluxed at 65 - 80 °C and atmospheric pressure in Dean-Stark configuration to remove methanol. The suspension is cooled to 31 - 35 °C and filtered, the cake washed with n-heptane (147.1 kg, 0.94 w/w), and the solid dried at 40 °C (101.0 kg, 93.8% uncorrected, 99.2% ee). $^1$H NMR (400 MHz, DMSO-d6) $\delta$ ppm -0.12 - 0.14 (m, 2 H) 0.26 - 0.42 (m, 2 H) 0.44 - 0.55 (m, 1 H) 1.70 - 1.83 (m, 2 H) 2.23 (d, *J*=1.52 Hz, 3 H) 4.24 (t, *J*=7.33 Hz, 1 H) 7.22 - 7.29 (m, 1 H) 7.29 - 7.36 (m, 1 H) 7.40 (dd, *J*=10.99, 1.39 Hz, 1 H). ESI-MS: 194.2 $[M+H]^+$, 177.0 $[M-NH_2]^+$.

Step 4: Preparation of (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyt-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (Compound 7-A)

**[0561]**



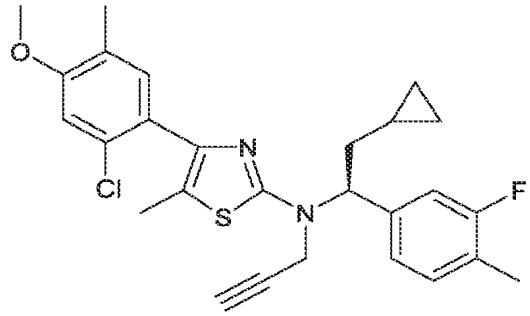

Compound 7-A

**[0562]** A mixture of n-heptane (146 kg), water (142 kg), Compound 5-A (57.4 kg), and aqueous sodium hydroxide (30% w/w, 41.0 kg) was stirred together. The layers were partitioned, and the aqueous layer removed. The organic layer was washed with water (170 kg) and the layers partitioned. The organic layer was set aside using n-heptane (40 kg) to rinse and n-heptane (145 kg) and 1-(2-chloro-4-methoxy-5-methylphenyl)-2-thiocyanatopropan-1-one (6-A, 66.1 kg) were added to the reactor and heated to 85 °C. The previously set aside organic layer containing the free base of Compound 5-A was added at 84 - 85 °C to the reactor and rinsed with n-heptane (20 kg). The resulting mixture was stirred for 2 h at 83 °C. Subsequently, the solvent was switched to methanol by four put-and-take additions/vacuum distillations of methanol (180 kg) at 55 °C with the target volume being 287 L remaining in the reactor. The suspension was cooled to 5 °C and water (570 kg) was added over 4 h at 5 - 10 °C, with the first 60 kg added very slowly. The suspension was aged 2 h at °C and then isolated by filtration and washed with a mixture of methanol/water (91/115 kg) and then a mixture of methanol/water (134/57 kg). The yellow solid was dried at 25 °C and 1 mbar for 17 h then 40 °C and 1 mbar for 22 h to afford Compound 7-A (97.4 kg, 87.5% yield). $^1$H NMR (400 MHz, DMSO-d6) $\delta$ ppm -0.01 - 0.14 (m, 2 H) 0.29 - 0.42 (m, 2 H) 0.61 - 0.73 (m, 1 H) 1.47 (dt, *J*=13.83, 6.85 Hz, 1 H) 1.76 (dt, *J*=13.89, 7.20 Hz, 1 H) 2.00 (s, 3 H) 2.11 (s, 3 H) 2.19 (d, *J*=1.01 Hz, 3 H) 3.82 (s, 3 H) 4.54 (q, *J*=7.58 Hz, 1 H) 7.00 (s, 1 H) 7.06 (d, *J*=0.76 Hz,

1H) 7.08 - 7.14 (m, 2 H) 7.18 - 7.23 (m, 1 H) 7.89 (d, *J*=8.08 Hz, 1 H). ESI-MS: 445.3 m/z $[M+H]^+$.

Step 5: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I))

**[0563]**



Compound of Formula (I)

**[0564]** A mixture of MTBE (279 kg), tetra-n-butylammonium bromide (10.5 kg), and Compound 7-A (95.4 kg) were heated at 60 °C external temperature for 30 min and then cooled to 0 °C. Aqueous potassium hydroxide (52.4% w/w, 364 kg) and propargyl bromide (39.4 kg as an 80% w/w solution in toluene, 1.19 eq.) were added at 0 - 5 °C and the biphasic mixture aged 14.5 h at 4 - 6 °C with vigorous stirring. Subsequently, water (191 kg) was added and the aqueous layer was discharged. The organic layer was washed twice with water (382 kg) and once with aqueous acetic acid (5.26% w/w, 190 kg) at 20 °C. The mixture is polish filtered, rinsed with ethanol (11 kg) and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol (300 kg) at 25 - 30 °C for the first cycle and then 35 - 40 °C with the target volume of each cycle being 250 L remaining in the reactor. Ethanol (164 kg) was added and the mixture heated at 60 °C external for 0.5 h before it was cooled to 25 °C in 1 h and seeded with authentic compound of Formula (I) (0.340 kg) which may be prepared as described below in Example 15B. The suspension was aged for 5 h, cooled to 0 °C in 2 h, aged 12 h, filtered, and washed twice with ethanol (24 kg each) precooled to 0 °C. The white solid was dried at 40 °C and 1 mbar for 19 h to yield 80.15 kg of the compound of Formula (I), Form I (77.2% yield). $^1$H NMR (400 MHz, DMSO-*d*6) $\delta$ ppm 0.14 (qt, *J*=8.59, 4.42 Hz, 2 H) 0.29 - 0.48 (m, 2 H) 0.61 - 0.82 (m, 1 H) 1.89 (dt, *J*=14.08, 6.98 Hz, 1 H), 2.07 (br d, *J*=7.83 Hz, 1 H) 2.10 (s, 3 H) 2.14 (s, 3 H) 2.20 (d, *J*=1.01 Hz, 3 H) 3.11 (t, *J*=2.27 Hz, 1 H) 3.83 (s, 3 H) 3.94 - 4.22 (m, 2 H) 5.26 (t, *J*=7.58 Hz, 1 H) 7.05 (s, 1 H) 7.10 ~ 7.36 (m, 4 H). ESI-MS: 483.2 m/z $[M+H]^+$.

**[0565]** The crystallinity of the crystalline free base Compound of Formula (I), Form I was confirmed by XRPD (Figure 25, Table 44) and further supported by DSC (Figure 26), indicating the crystalline compound having an onset of melt at about 84.4 °C (71.9 J/g). TGA of the crystalline free base exhibited about 0.6% of weight loss due to solvent/$H_2O$.

**Table 44. XRPD Peak Data for the Compound of Formula (I) Crystalline Free Base Form I**

| 2-Theta (°) | Height (cps) |
|---|---|
| 5.901(15) | 1221(101) |
| 10.367(11) | 1280(103) |
| 11.762(13) | 1377(107) |
| 12.582(11) | 1591(115) |
| 13.802(2) | 7326(247) |
| 14.1541(16) | 20179(410) |
| 15.173(14) | 449(61) |
| 15.854(7) | 2906(156) |
| 16.746(5) | 5113(206) |
| 18.366(7) | 1171(99) |

(continued)

| 2-Theta (°) | Height (cps) |
|---|---|
| 19.586(2) | 27789(481) |
| 20.100(4) | 10759(299) |
| 20.794(4) | 5441(213) |
| 21.730(5) | 7125(244) |
| 22.239(7) | 10370(294) |
| 23.056(11) | 3482(170) |
| 23.714(7) | 2300(138) |
| 24.115(7) | 8402(265) |
| 25.666(4) | 26173(467) |
| 26.296(6) | 1505(112) |
| 26.752(4) | 9919(288) |
| 27.264(7) | 1016(92) |
| 27.874(7) | 2092(132) |
| 28.623(3) | 10560(297) |
| 29.546(6) | 5811(220) |
| 30.025(3) | 2248(137) |
| 30.737(10) | 1333(105) |
| 31.017(19) | 1406(108) |
| 31.588(10) | 2292(138) |
| 31.809(8) | 2212(136) |
| 32.126(13) | 593(70) |
| 33.200(16) | 839(84) |
|  | 996(158) |
| 33.914(13) | 1156(98) |
| 34.276(16) | 1008(92 |
| 34.564(12) | 1056(94 |
| 35.397(18) | 816(82) |
| 36.073(10) | 1928(127) |
| 36.67(3) | 562(68) |
| 37.347(9) | 1553(114) |
| 37.776(12) | 1573(114) |
| 39.070(7) | 1890(125) |
| 39.743(15) | 1042(93) |
| 40.643(9) | 2808(153) |
| 41.106(8) | 1107(96) |
| 41.984(11) | 2686(150) |
| 42.376(16) | 986(91) |
| 42.901(16) | 492(64) |

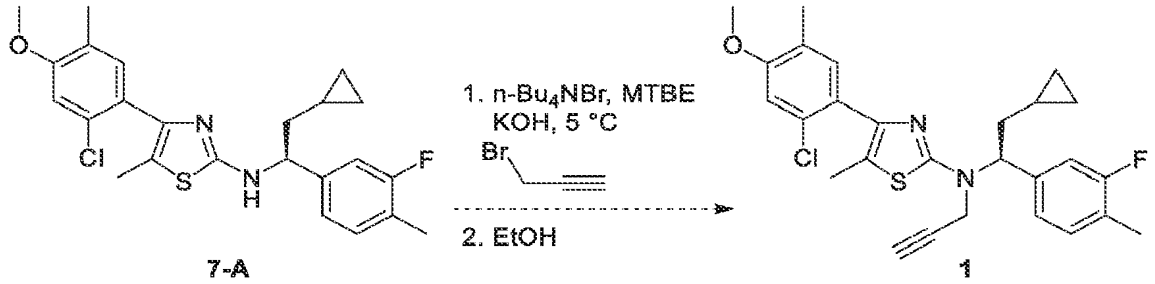
(continued)

| 2-Theta (°) | Height (cps) |
|---|---|
| 43.543(10) | 4744(199) |
| 44.419(16) | 2810(153) |

**Example 15B**

**Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1*S*)-2-cyclopropy1-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), seed batch)**

**[0566]**



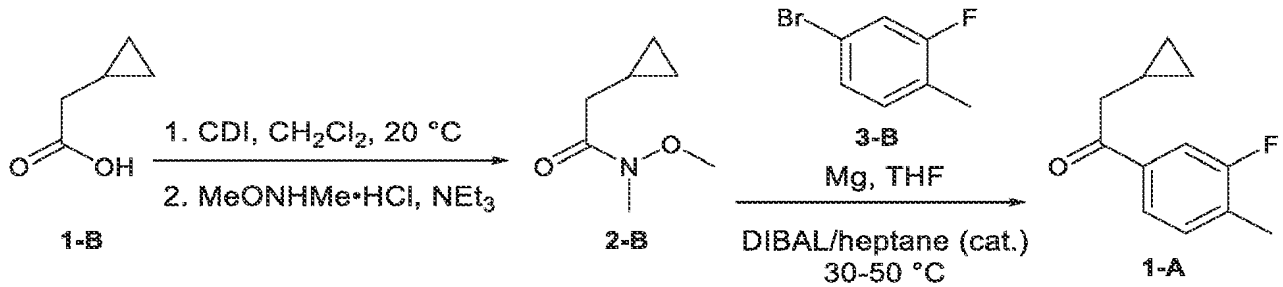

**[0567]** A mixture of MTBE, *tetra*-n-butylammonium bromide, and Compound 7-A cooled to 0 °C is treated with aqueous potassium hydroxide and propargyl bromide maintaining the temperature at 0 - 5 °C. The resulting biphasic mixture is aged 23 h at 4 - 6 °C. Subsequently, water and MTBE are added and the aqueous layer is discharged. The organic layer is washed twice with water and once with aqueous acetic acid at 20 °C. Ethanol is added and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol at 35 - 40 °C with a target volume of each cycle remaining in the vessel, except for the third cycle where the mixture is concentrated to dryness. Ethanol is added to the vessel and the mixture heated at 60 °C external for 0.5 h before it is cooled to 20 °C in 1 h and aged 18 h affording a suspension. The suspension is cooled to 0 °C, aged 6 h, filtered, and washed twice with ethanol pre-cooled to 0 °C to afford a solid. The solid is dried at 40 °C under vacuum to afford the compound of Formula (I).

**Example 15C**

**Scheme 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)**

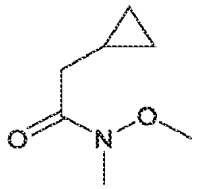
**[0568]**

Scheme 2




Step 1: Preparation of 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (Compound 2-B)

**[0569]**

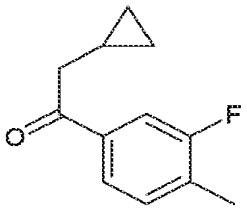


Compound 2-B

**[0570]** A suspension of 1,1'-Carbonyldiimidazole (152.6 kg, 1.01 eq.) in DCM (682 kg, 513 L, 7.3 w/w relative to 2-cyclopropylacetic acid) was treated with a solution of 2-cyclopropylacetic acid (1-B, 93.6 kg, 1 eq.) in DCM (248 kg, 186 L, 2.65 w/w) over at least 1 h, keeping the temperature ≤ 25 °C and compensating for significant effervescence. The resulting mixture is stirred for 15 min at 22 °C and then *N,O*-dimethylhydroxylamine•HCl (93.3 kg, 1.03 eq.) is added in portions, keeping the temperature ≤30 °C. Subsequently, triethylamine (46.4 kg, 0.49 eq.) is added to the stirring mixture at 20 - 25 °C. The resulting mixture is stirred at 22 °C at least 1 h. The mixture is washed once with $KHSO_4$ solution (0.24 M, 357.1 kg, 0.09 eq.), once with $KHSO_4$ solution (0.40 M, 365.4 kg, 0.15 eq.), once with $KHSO_4$ solution (0.80 M, 384.5 kg, 0.30 eq.), and once with $NaHCO_3$ solution (0.60 M, 393.1 kg, 0.24 eq.). Residual DCM is removed by three put-and-takes of THF (166.6 kg, 1.78 w/w) and vacuum distillation (50 - 60 °C, to minimum volume/until distillation stops). THF (333.2 kg. 3.56 w/w) is added and the yield is determined by correcting for the LOD and GC-FID purity of the sample (131.5 kg, 98.2% corrected). $^1$H-NMR (400 MHz, DMSO-d6) δ: - 0.01 - 0.03 (m, 2H) 0.32 - 0.36 (m, 2H) 0.81 - 0.90 (br m, 1H) 2.18 (d, *J*=6.80 Hz, 2H) 2.97 (s, 3 H) 3.53 (s, 3H). ESI-MS: 144.0 $[M+H]^+$.

Step 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)

**[0571]**



Compound 1-A

**[0572]** Mg (turnings, 28.6 kg, 1.37 eq.) are suspended in THF (244.7 kg, 2.0 w/w) and DIBAL-H (1 M in n-heptane, 18.9 kg, 0.03 eq.) is added dropwise at 30 °C, The resulting mixture is stirred at 30 °C for at least 10 min and then 4-bromo-2-fluoro-1-methylbenzene (3-B, neat, 21.1 kg, 0.13 eq.) is added over at least 30 min at 30 - 50 °C. Subsequently, the mixture is treated with a solution of 4-bromo-2-fluoro-1-methylbenzene (3-B, 191.6 kg, 1.18 eq.) in THF (414.5 kg, 3.37 w/w) at 30 - 50 °C over 3 h or less. The mixture is stirred at 30 °C for at least 1 h. Subsequently, the mixture is treated with 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (2-B, 123.0 kg, 1 eq., 25.9% w/w solution in THF) over at least 1 h at 15 - 25 °C. The resulting mixture is stirred at 20 - 25 °C for at least 1 h. The stirring mixture is then treated with aqueous HCl (3 M, 10.3% w/w, 668.9 kg, 2.24 eq.) at 10 - 25 °C and the resulting mixture is stirred at least 2 h (check pH 3.0 - 3.5). The layers are separated, and the aqueous layer is combined with heptane (290.3 kg, 2.36 w/w). The layers are separated, and the organic layer is washed once with $NaHCO_3$ solution (0.63 M, 211.6 kg, 0.15 eq.) and once with NaCl solution (2.57 M, 213.0 kg, 0.55 eq.). The residual solvents are removed by vacuum distillation at 58 - 62 °C until distillation stops and then one put-and-take of toluene (275.5 kg, 2.24 w/w) at 107 - 117 °C until distillation stops. Toluene (275.5 kg, 2.24 w/w) is added and the yield is determined by correcting for the LOD and GC-FID purity of the sample (150.7 kg, 91.3% corrected). $^1$H NMR (400 MHz, DMSO-*d*6) δ ppm 0.07 - 0.21 (m, 2 H) 0.40 - 0.54 (m, 2 H) 1.02 (ttt, *J*=8.16, 8.16, 6.68, 6.68, 4.86, 4.86 Hz, 1 H) 2.30 (d, *J*=1.77 Hz, 3 H) 2.91 (d, *J*=6.57 Hz, 2 H) 7.44 (t, *J*=7.83 Hz, 1 H) 7.57 - 7.78 (m, 2 H). ESI-MS: 193.1 $[M+H]^+$.

**Example 16: Compound of Formula (I) Crystalline Tosylate Salt Form 1**

**[0573]** Approximately 20 mg of the Compound of Formula (I) was weighed into a vial. Using a positive displacement

pipette, 250 μL of solvent (IPA) was added to the vial along with a stir bar. The vial was placed in an aluminum block on a Reacti-Therm mixer and heated to 60 °C for ~1 hour. A molar equivalent of para-toluenesulfonic acid was added to the vial (20 μL of a 2M solution in water) and allowed to stir. The sample was slow cooled back to room temperature along with mild Nitrogen gas for evaporation. Precipitate was collected, left to dry overnight, and then analyzed by XRPD, DSC, and TGA.

**[0574]** The crystallinity of the crystalline tosylate form 1 was confirmed by XRPD (Figure 27, Table 45) and further supported by DSC (Figure 28), indicating the crystalline compound having an onset of melt at about 156 °C (22.2 J/g). TGA of the crystalline compound is provided in Figure 28, and exhibited about 0.5% of weight loss due to solvent/$H_2O$.

**Table 45. XRPD Peak Data for the Compound of Formula (I) Crystalline Tosylate Form 1**

| 2-Theta (°) | Height (cps) |
|---|---|
| 8.112(9) | 957(89) |
| 9.124(2) | 12296(320) |
| 9.471(2) | 4519(194) |
| 10.525(3) | 8507(266) |
| 11.316(3) | 10211(292) |
| 13.182(5) | 6158(227) |
| 13.494(6) | 1598(115) |
| 14.249(9) | 2197(135) |
| 15.208(9) | 1746(121) |
| 15.711(7) | 1437(109) |
| 16.252(5) | 5723(218) |
| 16.692(3) | 3848(179) |
| 17.540(4) | 1578(115) |
| 19.031(6) | 6774(238) |
| 19.265(4) | 6491(233) |
| 19.499(10) | 3152(162) |
| 20.401(3) | 8581(267) |
| 20.656(4) | 3040(159) |
| 21.142(3) | 11498(310) |
| 21.703(6) | 4979(204) |
| 21.870(11) | 5331(211) |
| 22.277(5) | 3701(176) |
| 22.769(3) | 10159(291) |
| 23.297(3) | 14954(353) |
| 23.532(4) | 3597(173) |
| 23.810(3) | 9590(283) |
| 24.73(2) | 2325(139) |
| 25.47(4) | 1704(119) |
| 26.087(5) | 2413(142) |
| 26.71(3) | 422(59) |
| 27.210(6) | 1648(117) |
| 27.593(5) | 2825(153) |

(continued)

| 2-Theta (°) | Height (cps) |
|---|---|
| 28.472(4) | 6417(231) |
| 29.51(3) | 1423(109) |
| 29.98(3) | 849(84) |
| 30.63(6) | 1262(103) |
| 30.77(3) | 1121(97) |
| 31.577(3) | 5563(215) |
| 32.74(4) | 874(85) |
| 33.73(4) | 1111(96) |
| 34.415(13) | 2054(131) |
| 34.799(11) | 706(77) |
| 35.139(15) | 1320(105) |
| 35.682(16) | 1028(93) |
| 38.39(4) | 751(79) |
| 39.743(17) | 1790(122) |
| 40.219(16) | 762(80) |
| 41.23(3) | 925(88) |
| 43.16(3) | 1540(113) |
| 44.288(12) | 1142(98) |

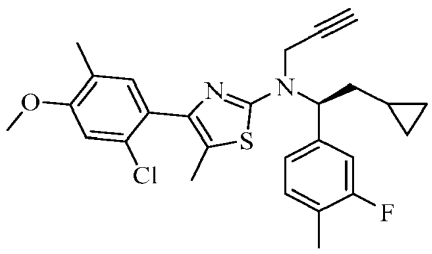
## OTHER EMBODIMENTS

**[0575]** It is to be understood that the foregoing description is intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

**[0576]** The following numbered paragraphs set out preferred features and preferred combinations of features of the present invention:

1. A pharmaceutical composition comprising:

(a) a compound of Formula (I):




(I)

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

2. The pharmaceutical composition of paragraph 1, comprising about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

3. The pharmaceutical composition of paragraph 1, comprising about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

4. The pharmaceutical composition of paragraph 1, comprising about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

5. The pharmaceutical composition of any one of paragraphs 1-4, comprising an oily phase vehicle.

6. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 1 wt% to about 50 wt% of the oily phase vehicle.

7. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 20 wt% to about 50 wt% of the oily phase vehicle.

8. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 35 wt% to about 45 wt% of the oily phase vehicle.

9. The pharmaceutical composition of any one of paragraphs 1-5, comprising about 39 wt% of the oily phase vehicle.

10. The pharmaceutical composition of any one of paragraphs 1-9, wherein the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

11. The pharmaceutical composition of any one of paragraphs 1-10, wherein the oily phase vehicle is medium-chain triglycerides.

12. The pharmaceutical composition of any one of paragraphs 10-11, wherein the medium-chain triglycerides are Labrafac TM Lipophile WL1349.

13. The pharmaceutical composition of any one of paragraphs 10-11, wherein the medium-chain triglycerides are Miglyol 812N.

14. The pharmaceutical composition of any one of paragraphs 1-13, comprising an emulsifying agent.

15. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 5 wt% to about 50 wt% of the emulsifying agent.

16. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 10 wt% to about 30 wt% of the emulsifying agent.

17. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 15 wt% to about 25 wt% of the emulsifying agent.

18. The pharmaceutical composition of any one of paragraphs 1-14, comprising about 20 wt% of the emulsifying agent.

19. The pharmaceutical composition of any one of paragraphs 1-18, wherein the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

20. The pharmaceutical composition of any one of paragraphs 1-19, wherein the emulsifying agent is propylene glycol dicaprylate/dicaprate.

21. The pharmaceutical composition of any one of paragraphs 19-20, wherein the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

22. The pharmaceutical composition of any one of paragraphs 1-21, comprising a nonionic surfactant.

23. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 5 wt% to about 50 wt% of the nonionic surfactant.

24. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 10 wt% to about 30 wt% of the nonionic surfactant.

25. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 15 wt% to about 25 wt% of the nonionic surfactant.

26. The pharmaceutical composition of any one of paragraphs 1-22, comprising about 19 wt% of the nonionic surfactant.

27. The pharmaceutical composition of any one of paragraphs 1-26, wherein the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides.

28. The pharmaceutical composition of any one of paragraphs 1-27, wherein the nonionic surfactant is lauroyl polyoxyl-32 glycerides.

29. The pharmaceutical composition of any one of paragraphs 27-28, wherein the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.

30. The pharmaceutical composition of any one of paragraphs 1-29, comprising a solubilizing agent.

31. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 1 wt% to about 50 wt% of the solubilizing agent.

32. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 1 wt% to about 20 wt% of the solubilizing agent.

33. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 5 wt% to about 15 wt% of the solubilizing agent.

34. The pharmaceutical composition of any one of paragraphs 1-30, comprising about 11 wt% of the solubilizing agent.

35. The pharmaceutical composition of any one of paragraphs 1-34, wherein the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer.

36. The pharmaceutical composition of any one of paragraphs 1-35, wherein the solubilizing agent is vitamin E polyethylene glycol succinate.

37. The pharmaceutical composition of any one of paragraphs 35-36, wherein the vitamin E polyethylene glycol succinate is Kolliphor® TPGS.

38. The pharmaceutical composition of any one of paragraphs 35-36, wherein the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.

39. The pharmaceutical composition of paragraph 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) an oily phase vehicle;
(c) an emulsifying agent;
(d) a nonionic surfactant; and
(e) a solubilizing agent.

40. The pharmaceutical composition of paragraph 1, comprising:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 35 wt% to about 45 wt% of an oily phase vehicle;
(c) about 15 wt% to about 25 wt% of an emulsifying agent;
(d) about 15 wt% to about 25 wt% of a nonionic surfactant; and
(e) about 5 wt% to about 15 wt% of a solubilizing agent.

41. The pharmaceutical composition of paragraph 1, comprising:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 39 wt% of an oily phase vehicle;
(c) about 20 wt% of an emulsifying agent;
(d) about 19 wt% of a nonionic surfactant; and
(e) about 11 wt% of a solubilizing agent.

42. The pharmaceutical composition of paragraph 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) a medium-chain triglycerides component;
(c) a propylene glycol dicaprylate/dicaprate component;
(d) a lauroyl polyoxyl-32 glycerides component; and
(e) a vitamin E polyethylene glycol succinate component.

43. The pharmaceutical composition of paragraph 1, comprising:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) about 35 wt% to about 45 wt% of medium-chain triglycerides;
(c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;
(d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and
(e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.

44. The pharmaceutical composition of paragraph 1, comprising:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;
(b) about 39 wt% of medium-chain triglycerides;
(c) about 20 wt% of propylene glycol dicaprylate/dicaprate;
(d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and
(e) about 11 wt% of vitamin E polyethylene glycol succinate.

45. The pharmaceutical composition of any one of paragraphs 1-44, wherein the compound of Formula (I), or pharmaceutically acceptable salt thereof, is in crystalline form.

46. The pharmaceutical composition of any one of paragraphs 1-45, comprising the compound of Formula (I) as a free base.

47. The pharmaceutical composition of paragraph 45, wherein the crystalline form comprises Form I of the compound of Formula (I).

48. The pharmaceutical composition of any one of paragraphs 1-47, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to

about 200 mg, based on the weight of the free base.

49. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg, based on the weight of the free base.

50. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg, based on the weight of the free base.

51. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg, based on the weight of the free base.

52. The pharmaceutical composition of paragraph 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg, based on the weight of the free base.

53. The pharmaceutical composition of any one of paragraphs 1-52, that is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

54. The pharmaceutical composition of any one of paragraphs 48-53, wherein the pharmaceutical composition is in tablet form.

55. The pharmaceutical composition of any one of paragraphs 48-53, wherein the pharmaceutical composition is in capsule form.

56. The pharmaceutical composition of any one of paragraphs 48-55, wherein the dosage form is coated.

57. A method for preparing the pharmaceutical composition of any one of paragraphs 1-56, comprising:

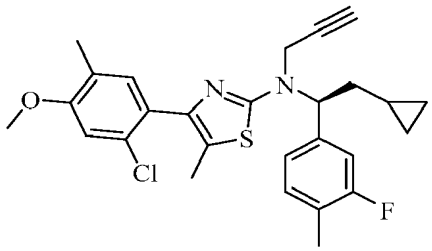
(a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;
(b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

58. The method of paragraph 57, further comprising:

(d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and
(e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

59. A pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):




(I)

or a pharmaceutically acceptable salt thereof;
(b) one or more of a sweetener, an anti-oxidant, and a flavor; and
(c) a liquid vehicle.

60. The pharmaceutical composition of paragraph 59, comprising about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

61. The pharmaceutical composition of paragraph 59, comprising about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

62. The pharmaceutical composition of paragraph 59, comprising about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

63. The pharmaceutical composition of any one of paragraphs 59-62, comprising a sweetener.

64. The pharmaceutical composition of any one of paragraphs 59-63, comprising about 0.01 w/v% to about 1.5 w/v% of the sweetener.

65. The pharmaceutical composition of any one of paragraphs 59-63, comprising about 0.1 w/v% to about 0.5 w/v% of the sweetener.

66. The pharmaceutical composition of any one of paragraphs 59-63, comprising about 0.15 w/v% of the sweetener.

67. The pharmaceutical composition of any one of paragraphs 59-66, wherein the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and avantame.

68. The pharmaceutical composition of any one of paragraphs 59-67, wherein the sweetener is saccharin.

69. The pharmaceutical composition of any one of paragraphs 59-68, comprising an anti-oxidant.

70. The pharmaceutical composition of any one of paragraphs 59-69, comprising about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant.

71. The pharmaceutical composition of any one of paragraphs 59-69, comprising about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant.

72. The pharmaceutical composition of any one of paragraphs 59-69, comprising about 0.17 w/v% of the anti-oxidant.

73. The pharmaceutical composition of any one of paragraphs 59-72, wherein the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid.

74. The pharmaceutical composition of any one of paragraphs 59-73, wherein the anti-oxidant is butylated hydroxytoluene.

75. The pharmaceutical composition of any one of paragraphs 59-74, comprising a flavor.

76. The pharmaceutical composition of any one of paragraphs 59-75, comprising about 0.01 w/v% to about 0.5 w/v% of the flavor.

77. The pharmaceutical composition of any one of paragraphs 59-75, comprising about 0.05 w/v% to about 0.2 w/v% of the flavor.

78. The pharmaceutical composition of any one of paragraphs 59-75, comprising about 0.10 w/v% of the flavor.

79. The pharmaceutical composition of any one of paragraphs 59-78, wherein the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetrarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor.

80. The pharmaceutical composition of any one of paragraphs 59-79, wherein the flavor is FONA orange flavor.

81. The pharmaceutical composition of any one of paragraphs 59-80, comprising about 50 w/v% to about 99.9 w/v%

of the liquid vehicle.

82. The pharmaceutical composition of any one of paragraphs 59-80, comprising about 92 w/v% to about 97 w/v% of the liquid vehicle.

83. The pharmaceutical composition of any one of paragraphs 59-80, comprising about 94.6 w/v% of the liquid vehicle.

84. The pharmaceutical composition of any one of paragraphs 59-83, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

85. The pharmaceutical composition of any one of paragraphs 59-84, wherein the liquid vehicle is medium-chain triglycerides.

86. The pharmaceutical composition of any one of paragraphs 84-85, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

87. The pharmaceutical composition of any one of paragraphs 59-86, further comprising a surfactant.

88. The pharmaceutical composition of paragraph 87, comprising about 1 w/v% to about 50 w/v% of the surfactant.

89. The pharmaceutical composition of paragraph 87, comprising about 10 w/v% to about 30 w/v% of the surfactant.

90. The pharmaceutical composition of paragraph 87, comprising about 20 w/v% of the surfactant.

91. The pharmaceutical composition of any one of paragraphs 87-90, wherein the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters.

92. The pharmaceutical composition of any one of paragraphs 87-91, wherein the surfactant is oleoyl polyoxyl-6 glycerides.

93. The pharmaceutical composition of any one of paragraphs 91-92, wherein the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

94. The pharmaceutical composition of any one of paragraphs 59-93, comprising about 70 w/v% to about 80 w/v% of the liquid vehicle.

95. The pharmaceutical composition of any one of paragraphs 59-93, comprising about 75 w/v% of the liquid vehicle.

96. The pharmaceutical composition of any one of paragraphs 59-95, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

97. The pharmaceutical composition of any one of paragraphs 59-96, wherein the liquid vehicle is medium-chain triglycerides.

98. The pharmaceutical composition of any one of paragraphs 95-96, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

99. The pharmaceutical composition of paragraph 59, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) a sweetener;
(c) an anti-oxidant;
(d) a flavor; and

(e) a liquid vehicle.

100. The pharmaceutical composition of paragraph 99, further comprising a surfactant.

101. The pharmaceutical composition of paragraph 59, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
(d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and
(e) about 92 w/v% to about 97 w/v% of a liquid vehicle.

102. The pharmaceutical composition of paragraph 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of a sweetener;
(c) about 0.17 w/v% of an anti-oxidant;
(d) about 0.1 w/v% of a flavor; and
(e) about 94.6 w/v% of a liquid vehicle.

103. The pharmaceutical composition of paragraph 59, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
(d) about 0.05 w/v% to about 0.2 w/v% of a flavor;
(e) about 15 w/v% to about 25 w/v% of a surfactant; and
(f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

104. The pharmaceutical composition of paragraph 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of a sweetener;
(c) about 0.17 w/v% of an anti-oxidant;
(d) about 0.1 w/v% of a flavor;
(e) about 20 w/v% of a surfactant; and
(f) about 75 w/v% of a liquid vehicle.

105. The pharmaceutical composition of paragraph 59, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) saccharin;
(c) butylated hydroxytoluene;
(d) FONA orange flavor; and
(e) medium-chain triglycerides.

106. The pharmaceutical composition of paragraph 105, further comprising oleoyl polyoxyl-6 glycerides.

107. The pharmaceutical composition of paragraph 106, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and
(e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

108. The pharmaceutical composition of paragraph 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of saccharin;
(c) about 0.17 w/v% of butylated hydroxytoluene;
(d) about 0.1 w/v% of FONA orange flavor; and
(e) about 94.6 w/v% of medium-chain triglycerides.

109. The pharmaceutical composition of paragraph 59, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1 S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;
(e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and
(f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

110. The pharmaceutical composition of paragraph 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of saccharin;
(c) about 0.17 w/v% of butylated hydroxytoluene;
(d) about 0.1 w/v% of FONA orange flavor;
(e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and
(f) about 75 w/v% of medium-chain triglycerides.

111. The pharmaceutical composition of any one of paragraphs 59-110, comprising the compound of Formula (I) as a free base.

112. The pharmaceutical composition of any one of paragraphs 59-111, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base.

113. The pharmaceutical composition of paragraph 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base.

114. The pharmaceutical composition of paragraph 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg/mL, based on the weight of the free base.

115. The pharmaceutical composition of paragraph 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg/mL, based on the weight of the free base.

116. The pharmaceutical composition of any one of paragraphs 1-56, having a viscosity between about 15 to about

40 centipoise at about 45 °C.

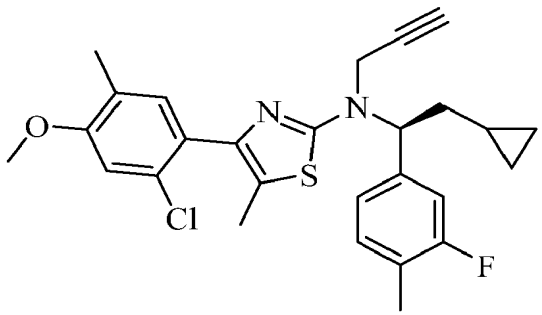
117. A method for preparing the pharmaceutical composition of any one of paragraphs 59-116, comprising:

(a) mixing a liquid vehicle with a sweetener;
(b) mixing the mixture of step (a) with an anti-oxidant and a flavor;
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and
(d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

118. The method of paragraph 117, wherein step (a) comprises mixing a liquid vehicle with a sweetener and a surfactant.

119. A spray-dried dispersion comprising:

a compound having the structure of Formula (I):




(I)

or a pharmaceutically acceptable salt thereof; and
a polymer selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer;
wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:1 to about 1:9.

120. The spray-dried dispersion of paragraph 119, wherein the neutral polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

121. The spray-dried dispersion of paragraph 119, wherein the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer.

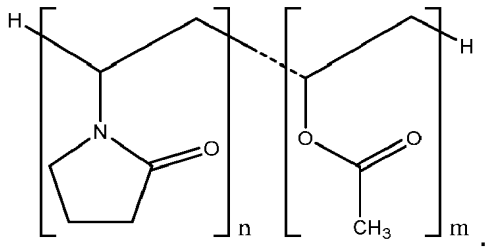
122. The spray-dried dispersion of paragraph 119, wherein the pyrrolidone polymer is selected from polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone vinyl acetate (PVP/VA).

123. The spray-dried dispersion of paragraph 122, wherein the pyrrolidone polymer is PVP/VA.

124. The spray-dried dispersion of paragraph 123, wherein the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 40:60 to about 60:40 by weight.

125. The spray-dried dispersion of paragraph 124, wherein the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight.

126. The spray-dried dispersion of any one of paragraphs 122-125, wherein the copolymer has the structure:



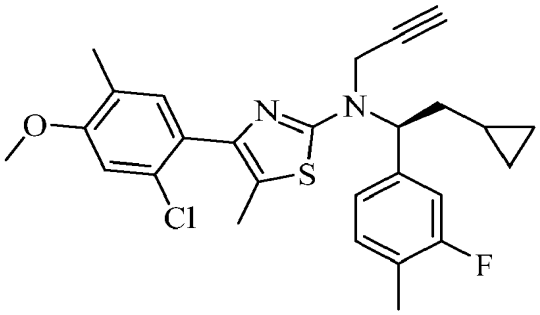
wherein the value of n is about 1 to about 2 times the value of m.

127. The spray-dried dispersion of paragraph 126, wherein the copolymer is copovidone, wherein the value of n is about 1.16 times the value of m.

128. The spray-dried dispersion of paragraph 126, wherein the copolymer is copovidone having an average molecular weight of about 45,000 to about 70,000.

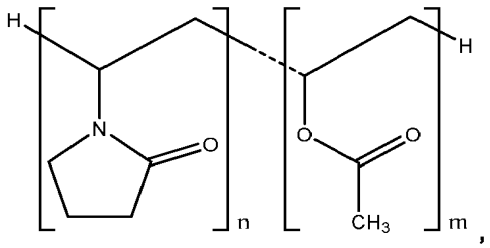
129. A spray-dried dispersion comprising:

a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and
a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



wherein the value of n is about 1 to about 2 times the value of m and the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight; and
wherein the weight ratio of the compound of Formula (I) to the copolymer is from about 1:1 to about 1:9.

130. The spray-dried dispersion of any one of paragraphs 119-129, wherein the compound of Formula (I) and the polymer together form homogeneous particles.

131. The spray-dried dispersion of any one of paragraphs 119-130, wherein the particles have a particle size distribution $D_{50}$ of about 5 μm to about 100 μm.

132. The spray-dried dispersion of any one of paragraphs 119-131, wherein the particles have a particle size distribution $D_{50}$ of about 10 μm to about 50 μm.

133. The spray-dried dispersion of any one of paragraphs 119-132, wherein the particles have a particle size distribution $D_{50}$ of about 15 μm to about 30 μm.

134. The spray-dried dispersion of any one of paragraphs 119-133, wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:1.5 to about 1:9.

135. The spray-dried dispersion of any one of paragraphs 119-134, wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:2.5 to about 1:4.

136. The spray-dried dispersion of any one of paragraphs 119-135, wherein the weight ratio of the compound of Formula (I) to the polymer is about 1:3.

137. The spray-dried dispersion of any one of paragraphs 119-136, wherein the particles have a residual solvent content less than about 2 wt %.

138. The spray-dried dispersion of any one of paragraphs 119-137, wherein the particles have a residual solvent content less than about 1 wt %.

139. The spray-dried dispersion of any one of paragraphs 119-138, wherein the particles have a residual solvent content of about 0.5 wt % or less.

140. The spray-dried dispersion of any one of paragraphs 119-139, wherein the compound of Formula (I) in the dispersion is substantially amorphous.

141. A pharmaceutical composition comprising the spray-dried dispersion of any one of paragraphs 119-140 and one or more pharmaceutically acceptable excipients.

142. The pharmaceutical composition of paragraph 141, wherein the spray-dried dispersion is present in an amount of about 20% to about 90% w/w of the composition.

143. The pharmaceutical composition of paragraph 142, wherein the spray-dried dispersion is present in an amount of about 40% to about 80% w/w of the composition.

144. The pharmaceutical composition of paragraph 141, wherein the spray-dried dispersion is present in an amount of about 1% to about 20% w/w of the composition.

145. The pharmaceutical composition of paragraph 144, wherein the spray-dried dispersion is present in an amount of about 13% w/w of the composition.

146. The pharmaceutical composition of any one of paragraphs 141-145, wherein the pharmaceutical excipients are selected from the group consisting of a filler, a lubricant, and combinations thereof.

147. The pharmaceutical composition of paragraph 146, wherein the filler is selected from the group consisting of a binder, a diluent, a disintegrant, a glidant, a surfactant, and combinations thereof.

148. The pharmaceutical composition of any one of paragraphs 141-147 formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg.

149. The pharmaceutical composition of paragraph 148, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg.

150. The pharmaceutical composition of paragraph 149, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg.

151. The pharmaceutical composition of paragraph 149, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg.

152. The pharmaceutical composition of any one of paragraphs 141-151, wherein the pharmaceutical excipients are selected from the group consisting of a glidant, a filler, a disintegrant, a lubricant, and a combination thereof.

153. The pharmaceutical composition of any one of paragraphs 141-152, comprising a glidant.

154. The pharmaceutical composition of any one of paragraphs 152-153, comprising about 0.1 w/w% to about 5 w/w% of the glidant.

155. The pharmaceutical composition of any one of paragraphs 152-153, comprising about 0.1 w/w% to about 1 w/w% of the glidant.

156. The pharmaceutical composition of any one of paragraphs 152-153, comprising about 0.67 w/w% of the glidant.

157. The pharmaceutical composition of any one of paragraphs 152-156, wherein the glidant is selected from calcium silicate, silicon dioxide, and talc.

158. The pharmaceutical composition of any one of paragraphs 152-157, wherein the glidant is calcium silicate.

159. The pharmaceutical composition of any one of paragraphs 141-158, comprising a filler.

160. The pharmaceutical composition of any one of paragraphs 152-159, comprising about 30 w/w% to about 99 w/w% of the filler.

161. The pharmaceutical composition of any one of paragraphs 152-159, comprising about 50 w/w% to about 90 w/w% of the filler.

162. The pharmaceutical composition of any one of paragraphs 152-159, comprising about 75.5 w/w% of the filler.

163. The pharmaceutical composition of any one of paragraphs 152-162, wherein the filler is selected from mannitol, microcrystalline cellulose, lactose, starch, isomalt, silicified microcrystalline cellulose, Dicalcium Phosphate, maltodextrin, and a combination thereof.

164. The pharmaceutical composition of any one of paragraphs 152-163, wherein the filler is a combination of mannitol and microcrystalline cellulose.

165. The pharmaceutical composition of any one of paragraphs 163-164, comprising about 30 w/w% to about 80 w/w% of mannitol.

166. The pharmaceutical composition of any one of paragraphs 163-164, comprising about 50 w/w% to about 60 w/w% of mannitol.

167. The pharmaceutical composition of any one of paragraphs 163-164, comprising about 56 w/w% of mannitol.

168. The pharmaceutical composition of any one of paragraphs 163-167, comprising about 1 w/w% to about 50 w/w% of microcrystalline cellulose.

169. The pharmaceutical composition of any one of paragraphs 163-167, comprising about 10 w/w% to about 30 w/w% of microcrystalline cellulose.

170. The pharmaceutical composition of any one of paragraphs 163-167, comprising about 20 w/w% of microcrystalline cellulose.

171. The pharmaceutical composition of any one of paragraphs 163-167, comprising about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose.

172. The pharmaceutical composition of any one of paragraphs 141-171, comprising a disintegrant.

173. The pharmaceutical composition of any one of paragraphs 152-172, comprising about 1 w/w% to about 30 w/w% of the disintegrant.

174. The pharmaceutical composition of any one of paragraphs 152-172, comprising about 5 w/w% to about 15 w/w% of the disintegrant.

175. The pharmaceutical composition of any one of paragraphs 152-172, comprising about 10 w/w% of the disintegrant.

176. The pharmaceutical composition of any one of paragraphs 152-175, wherein the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, and sodium bicarbonate.

177. The pharmaceutical composition of any one of paragraphs 152-176, wherein the disintegrant is croscarmellose sodium.

178. The pharmaceutical composition of any one of paragraphs 141-177, comprising a lubricant.

179. The pharmaceutical composition of any one of paragraphs 152-178, comprising about 0.1 w/w% to about 10 w/w% of the lubricant.

180. The pharmaceutical composition of any one of paragraphs 152-178, comprising about 0.1 w/w% to about 1 w/w% of the lubricant.

181. The pharmaceutical composition of any one of paragraphs 152-178, comprising about 0.5 w/w% of the lubricant.

182. The pharmaceutical composition of any one of paragraphs 152-181, wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid, sodium lauryl sulfate, sodium oleate, glyceryl behenate, and talc.

183. The pharmaceutical composition of any one of paragraphs 152-182, wherein the lubricant is sodium stearyl fumarate.

184. The pharmaceutical composition of any one of paragraphs 141-183, comprising:

(a) the spray-dried dispersion of any one of paragraphs 119-140;
(b) a glidant;
(c) a filler; and
(d) a disintegrant.

185. The pharmaceutical composition of any one of paragraphs 141-183, comprising:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of any one of paragraphs 119-140;
(b) about 0.1 w/w% to about 1 w/w% of a glidant;
(c) about 50 w/w% to about 90 w/w% of a filler; and
(d) about 5 w/w% to about 0.2 w/w% of a disintegrant.

186. The pharmaceutical composition of any one of paragraphs 141-183, comprising:

(a) about 13 w/w% of the spray-dried dispersion of any one of paragraphs 119-140;
(b) about 0.67 w/w% of a glidant;
(c) about 75.5 w/w% of a filler; and
(d) about 10 w/w% of a disintegrant.

187. The pharmaceutical composition of any one of paragraphs 141-183, comprising:

(a) the spray-dried dispersion of Example 3;

(b) calcium silicate;
(c) a combination of mannitol and microcrystalline cellulose; and
(d) croscarmellose sodium.

188. The pharmaceutical composition of paragraph 187, comprising:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of Example 3;
(b) about 0.1 w/w% to about 1 w/w% of calcium silicate;
(c) about 50 w/w% to about 60 w/w% of mannitol and about 10 w/w% to about 30 w/w% of microcrystalline cellulose; and
(d) about 5 w/w% to about 0.2 w/w% of croscarmellose sodium.

189. The pharmaceutical composition of paragraph 188, comprising:

(a) about 13 w/w% of the spray-dried dispersion of Example 3;
(b) about 0.67 w/w% of calcium silicate;
(c) about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose; and
(d) about 10 w/w% of croscarmellose sodium.

190. The pharmaceutical composition of any one of paragraphs 141-189 that is formulated as a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

191. The pharmaceutical composition of paragraph 190, wherein the pharmaceutical composition is in tablet form.

192. The pharmaceutical composition of paragraph 190, wherein the pharmaceutical composition is in capsule form.

193. The pharmaceutical composition of paragraph 190, wherein the pharmaceutical composition is in sachet form.

194. The pharmaceutical composition of paragraph 190, wherein the pharmaceutical composition is in granule form.

195. The pharmaceutical composition of any one of paragraphs 190-192, wherein the pharmaceutical composition is coated.

196. A method for preparing the spray-dried dispersion of any one of paragraphs 119-140, comprising:

dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and
spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer.

197. The method of paragraph 196, comprising removing the organic solvent after formation of the spray-dried dispersion by drying the spray-dried dispersion.

198. The method of paragraph 197, wherein the spray-dried dispersion is dried with a convection tray dryer.

199. The method of any one of paragraphs 196-198, wherein the organic solvent is acetone.

200. The method of any one of paragraphs 196-199, wherein the spray dryer inlet temperature is about 60°C to about 80°C.

201. The method of paragraph 200, wherein the spray dryer inlet temperature is about 72°C.

202. The method of any one of paragraphs 196-201, wherein the spray dryer outlet temperature is about 25°C to about 45°C.

203. The method of paragraph 202, wherein the spray dryer outlet temperature is about 35°C.

204. The method of any one of paragraphs 196-203, wherein the homogeneous particles comprise a bulk density of less than about 0.2 g/mL.

205. The method of paragraph 204, wherein the homogeneous particles comprise a bulk density of less than about 0.15 g/mL.

206. The method of any one of paragraphs 196-205, wherein the homogeneous particles comprise a tapped density of less than about 0.3 g/mL.

207. The method of paragraph 206, wherein the homogeneous particles comprise a tapped density of less than about 0.25 g/mL.

208. A method for preparing a pharmaceutical composition, comprising combining the spray-dried dispersion of any one of paragraphs 119-140 with one or more pharmaceutically acceptable excipients.

209. The method of paragraph 208, comprising:

(a) blending the spray-dried dispersion of any one of paragraphs 119-140, with a glidant;
(b) further blending the blend of step (a) with a filler and a disintegrant;
(c) screening the blend of step (b) to break up aggregates and assist with blend uniformity;
(d) further blending the intragranular blend of step (c);
(e) compaction of the intragranular blend of step (d) via roller compaction to form granules; and
(f) milling of ribbon from roller compaction into granules of step (e).

210. A method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the spray-dried dispersion of any one of paragraphs 119-140 or the pharmaceutical composition of any one of paragraphs 141-195.

211. The method of paragraph 210, wherein the spray-dried dispersion or the pharmaceutical composition is administered to the subject in a fed state.

212. The method of paragraph 210 or paragraph 211, wherein the spray-dried dispersion or the pharmaceutical composition is administered to the subject with a nutritional composition.

213. The method of paragraph 212, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

214. The method of paragraph 212 or paragraph 213, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

215. The method of any one of paragraphs 212-214, wherein the nutritional composition is administered within 30 minutes of administration of the spray-dried dispersion or the pharmaceutical composition.

216. The method of any one of paragraphs 211-215, wherein administering the spray-dried dispersion or the pharmaceutical composition exhibits a positive food effect.

217. The method of paragraph 216, wherein the positive food effect is measured in terms of $C_{max}$, AUC, or combinations thereof when comparing oral administration of the spray-dried dispersion or pharmaceutical composition in the fed and fasting states.

218. The method of any one of paragraphs 211-217, wherein the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10.

219. The method of any one of paragraphs 211-217, wherein the ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state is about 5 to about 10.

220. The method of any one of paragraphs 210-219, wherein the subject is a pediatric subject.

221. A method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, comprising orally administering to the subject the pharmaceutical composition of any one of paragraphs 141-195, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

222. The method of paragraph 221, wherein the subject is a pediatric subject.

223. A method of improving oral bioavailability of a compound of Formula (I) in a subject, comprising orally administering to the subject the pharmaceutical composition of any one of paragraphs 141-195, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

224. The method of paragraph 223, wherein the subject is a pediatric subject.

225. The spray-dried dispersion of any one of paragraphs 119-140, wherein the spray-dried dispersion is formulated for oral administration and exhibits a positive food effect when administered orally.

226. The spray-dried dispersion of paragraph 225, wherein the spray-dried dispersion has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10.

227. The spray-dried dispersion of paragraph 225, wherein the spray-dried dispersion has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 5 to about 10.

228. A crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

229. The salt of paragraph 228, having Form 1 of the Compound of Formula (I).

230. The salt of paragraph 228 or paragraph 229, having an X-ray powder diffraction pattern as substantially shown in Figure 27.

231. The salt of any one of paragraphs 228-230, having a DSC thermogram substantially as depicted in Figure 28.

232. The salt of any one of paragraphs 228-231, having a thermogravimetric analysis (TGA) thermogram substantially as depicted in Figure 28.

233. The salt of any one of paragraphs 228-232, having at least one X-ray powder diffraction (XRPD) peak, in terms of 2-theta (± 0.2 degrees), selected 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

234. The salt of any one of paragraphs 228-232, having at least two X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

235. The salt of any one of paragraphs 228-232, having at least three X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

236. The salt of any one of paragraphs 228-232, having at least four X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

237. The salt of any one of paragraphs 228-232, having characteristic X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), at 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

238. The salt of any one of paragraphs 228-237, having an endothermic peak having an onset of melt at about 156 °C (22.2 J/g) in a differential scanning calorimetry (DSC) thermogram.

239. A method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone

(ACTH); and (c) androstenedione in the subject.

240. The method of paragraph 239, wherein the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

241. The method of paragraph 240, wherein the circadian release occurs between the hours of 2 a.m. and 10 a.m.

242. The method of any one of paragraphs 239-241, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

243. The method of any one of paragraphs 239-242, wherein the level of 17-hydroxyprogesterone is reduced by at least 25%.

244. The method of any one of paragraphs 239-242, wherein the level of 17-hydroxyprogesterone is reduced by at least 50%.

245. The method of any one of paragraphs 239-244, wherein the level of adrenocorticotropic hormone is reduced by at least 25%.

246. The method of any one of paragraphs 239-244, wherein the level of adrenocorticotropic hormone is reduced by at least 40%.

247. The method of any one of paragraphs 239-244, wherein the level of adrenocorticotropic hormone is reduced by at least 50%.

248. The method of any one of paragraphs 239-247, wherein the level of androstenedione is reduced by at least 25%.

249. The method of any one of paragraphs 239-247, wherein the level of androstenedione is reduced by at least 30%.

250. The method of any one of paragraphs 239-247, wherein the level of androstenedione is reduced by at least 50%.

251. The method of any one of paragraphs 239-250, wherein the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

252. The method of any one of paragraphs 239-251, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

253. The method of any one of paragraphs 239-252, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

254. A method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of androstenedione in the subject.

255. The method of paragraph 254, wherein the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

256. The method of paragraph 254 or 255, wherein the androstenedione is reduced by at least 25%.

257. The method of paragraph 254 or 255, wherein the androstenedione is reduced by at least 30%.

258. The method of paragraph 254 or 255, wherein the androstenedione is reduced by at least 50%.

259. A method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

260. The method of paragraph 259, wherein the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

261. A method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

262. The method of paragraph 261, wherein the corticosteroid is a glucocorticoid.

263. A method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof,
wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

264. The method of any one of paragraphs 259-263, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

265. The method of any one of paragraphs 259-264, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

266. The method of any one of paragraphs 259-264, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

267. The method of any one of paragraphs 259-266, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

268. The method of any one of paragraphs 259-267, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-

2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

269. The method of any one of paragraphs 259-268, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

270. A method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

271. The method of paragraph 270, further comprising (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1-S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i).

272. The method of paragraph 271, further comprising (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

273. The method of paragraph 271 or 272, wherein steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window.

274. The method of any one of paragraphs 271-273, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m.

275. The method of any one of paragraphs 271-273, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

276. The method of any one of paragraphs 271-275, wherein steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

277. The method of any one of paragraphs 271-275, wherein steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

278. The method of any one of paragraphs 270-277, wherein step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

279. The method of any one of paragraphs 270-278, wherein step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

280. The method of any one of paragraphs 270-279, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

281. The method of any one of paragraphs 270-279, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

282. The method of any one of paragraphs 270-281, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

283. A method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, where in the subject is in a fed state.

284. The method of paragraph 283, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition.

285. The method of paragraph 284, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

286. The method of paragraph 284 or 285, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

287. The method of any one of paragraphs 284-286, wherein the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

288. A pharmaceutical composition of any one of paragraphs 1-56, 59-116 or 141-195 for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

289. The pharmaceutical composition for use according to paragraph 288, wherein the subject is in a fed state.

290. The pharmaceutical composition for use according to paragraph 288 or paragraph 289, wherein the subject is administered the pharmaceutical composition with a nutritional composition.

291. The pharmaceutical composition for use according to paragraph 290, wherein the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%.

292. The pharmaceutical composition for use according to paragraph 290, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

293. The pharmaceutical composition for use according to any one of paragraphs 290-292, wherein the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces.

294. The pharmaceutical composition for use according to any one of paragraphs 290-293, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

295. The pharmaceutical composition for use according to any one of paragraphs 290-294, wherein the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

296. The pharmaceutical composition for use according to any one of paragraphs 289-295, wherein administering the pharmaceutical composition exhibits a positive food effect.

297. The pharmaceutical composition for use according to paragraph 296, wherein the positive food effect is meas-

ured in terms of $C_{max}$, AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.

298. The pharmaceutical composition for use according to any one of paragraphs 289-297, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

299. The pharmaceutical composition for use according to any one of paragraphs 289-297, wherein the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

300. The pharmaceutical composition for use according to any one of paragraphs 289-297, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

301. The pharmaceutical composition for use according to any one of paragraphs 289-297, wherein the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

302. The pharmaceutical composition for use according to any one of paragraphs 288-301, wherein the subject is a pediatric subject.

303. The pharmaceutical composition for use according to any one of paragraphs 289-295, wherein the pharmaceutical composition exhibits a positive food effect when administered orally.

304. The pharmaceutical composition for use according to paragraph 303, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10.

305. The pharmaceutical composition for use according to paragraph 303, wherein the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 1 to about 4 or about 5 to about 10.

306. The pharmaceutical composition for use according to paragraph 303, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3.

307. The pharmaceutical composition for use according to paragraph 303, wherein the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 1.5 to about 3.

308. The pharmaceutical composition for use according to any one of paragraphs 288-307, wherein the pharmaceutical composition is administered to the subject with a meal.

309. The pharmaceutical composition for use according to paragraph 308, wherein the meal is a high fat meal.

310. The pharmaceutical composition for use according to paragraph 308, wherein the meal is a low fat meal.

311. The pharmaceutical composition for use according to any one of paragraphs 308-310, wherein the pharmaceutical composition is administered within about 5 minutes after the start of the meal.

312. The pharmaceutical composition for use according to any one of paragraphs 308-311, wherein the meal is an evening meal.

313. The pharmaceutical composition for use according to any one of paragraphs 308-311, wherein the meal is a morning meal.

314. The pharmaceutical composition for use according to any one of paragraphs 308-313, wherein administering the pharmaceutical composition exhibits a positive food effect.

315. The pharmaceutical composition for use according to paragraph 314, wherein the positive food effect is measured in terms of $C_{max}$, AUC, or combinations thereof of the compound of Formula (I) when comparing oral admin-

istration of the pharmaceutical composition in the fed and fasting states.

316. The pharmaceutical composition for use according to any one of paragraphs 308-315, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

317. The pharmaceutical composition for use according to any one of paragraphs 308-316, wherein the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

318. The pharmaceutical composition for use according to any one of paragraphs 308-315, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

319. The pharmaceutical composition for use according to any one of paragraphs 308-315 or 318, wherein the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

320. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

321. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

322. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

323. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

324. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

325. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

326. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

327. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

328. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

329. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

330. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

331. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

332. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

333. The pharmaceutical composition for use according to any one of paragraphs 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

334. The pharmaceutical composition for use according to any one of paragraphs 288-333, wherein the subject is concurrently receiving a dose of a glucocorticoid.

335. The pharmaceutical composition for use according to paragraph 334, wherein the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate.

336. The pharmaceutical composition for use according to paragraph 334 or 335, wherein the glucocorticoid is cortisol (hydrocortisone).

337. The pharmaceutical composition for use according to paragraph 334 or 335, wherein the glucocorticoid is cortisone.

338. The pharmaceutical composition for use according to paragraph 334 or 335, wherein the glucocorticoid is prednisone.

339. The pharmaceutical composition for use according to any one of paragraphs 334-338, wherein the glucocorticoid dose is measured in hydrocortisone equivalents.

340. The pharmaceutical composition for use according to any one of paragraphs 334-339, wherein the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents.

341. The pharmaceutical composition for use according to any one of paragraphs 334-340, wherein the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition.

342. The pharmaceutical composition for use according to any one of paragraphs 334-340, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m$^2$/day as measured after a time period of administration of the pharmaceutical composition.

343. The pharmaceutical composition for use according to any one of paragraphs 334-340, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m$^2$/day as measured after a time period of administration of the pharmaceutical composition.

344. The pharmaceutical composition for use according to any one of paragraphs 334-340, wherein the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m$^2$/day as measured after a time period of administration of the pharmaceutical composition.

345. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition

346. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

347. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

348. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

349. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

350. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

351. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

352. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

353. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

354. The pharmaceutical composition for use according to any one of paragraphs 334-344, wherein the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

355. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.

356. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.

357. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

358. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition.

359. The pharmaceutical composition for use according to any one of paragraphs 288-358, wherein the level of adrenocorticotropic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

360. The pharmaceutical composition for use according to any one of paragraphs 288-358, wherein the level of adrenocorticotropic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

361. The pharmaceutical composition for use according to any one of paragraphs 288-358, wherein the level of adrenocorticotropic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

362. The pharmaceutical composition for use according to any one of paragraphs 288-358, wherein the level of adrenocorticotropic hormone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

363. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the pharmaceutical composition.

364. The pharmaceutical composition for use according to any one of paragraphs 288-363, wherein the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

365. The pharmaceutical composition for use according to any one of paragraphs 288-363, wherein the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

366. The pharmaceutical composition for use according to any one of paragraphs 288-363, wherein the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

367. The pharmaceutical composition for use according to any one of paragraphs 288-363, wherein the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

368. The pharmaceutical composition for use according to any one of paragraphs 288-363, wherein the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

369. The pharmaceutical composition for use according to any one of paragraphs 288-368, wherein the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

370. The pharmaceutical composition for use according to any one of paragraphs 288-368, wherein the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

371. The pharmaceutical composition for use according to any one of paragraphs 288-368, wherein the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

372. The pharmaceutical composition for use according to any one of paragraphs 288-368, wherein the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

373. The pharmaceutical composition for use according to any one of paragraphs 288-368, wherein the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

374. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition.

375. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

376. The pharmaceutical composition for use according to any one of paragraphs 288-354, wherein the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

377. The pharmaceutical composition for use according to any one of paragraphs 334-376, wherein the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition.

378. The pharmaceutical composition for use according to paragraph 377, wherein one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition.

379. The pharmaceutical composition for use according to any one of paragraphs 341-378, wherein the time period of administration is at least about 4 weeks.

380. The pharmaceutical composition for use according to any one of paragraphs 341-378, wherein the time period of administration is at least about 24 weeks.

381. The pharmaceutical composition for use according to any one of paragraphs 341-378, wherein the time period of administration is at least about one year.

382. The pharmaceutical composition for use according to any one of paragraphs 288-381, wherein the subject is a pediatric subject.

383. The pharmaceutical composition for use according to paragraph 382, wherein the pediatric subject is less than or equal to six years old.

384. The pharmaceutical composition for use according to paragraph 382, wherein the pediatric subject is greater than six years old and less than eleven years old.

385. The pharmaceutical composition for use according to paragraph 382, wherein the pediatric subject is greater than ten years old and less than fifteen years old.

386. The pharmaceutical composition for use according to paragraph 382, wherein the pediatric subject is greater than fourteen years old and less than nineteen years old.

387. The pharmaceutical composition for use according to any one of paragraphs 288-381, wherein the subject is an adult subject.

388. The pharmaceutical composition for use according to any one of paragraphs 387, wherein the adult subject is over eighteen years old.

389. The pharmaceutical composition for use according to any one of paragraphs 288-388, wherein the subject is female.

390. The pharmaceutical composition for use according to any one of paragraphs 288-388, wherein the subject is male.

391. The pharmaceutical composition for use according to any one of paragraphs 288-390, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

392. The pharmaceutical composition for use according to any one of paragraphs 288-390, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid salt of any one of paragraphs 228-238.

393. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or a pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

394. The compound of paragraph 393, wherein the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

395. The compound of paragraph 394, wherein the circadian release occurs between the hours of 2 a.m. and 10 a.m.

396. The compound of any one of paragraphs 393-395, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

397. The compound of any one of paragraphs 393-396, wherein the level of 17-hydroxyprogesterone is reduced by at least 25%.

398. The compound of any one of paragraphs 393-396, wherein the level of 17-hydroxyprogesterone is reduced by at least 50%.

399. The compound of any one of paragraphs 393-398, wherein the level of adrenocorticotropic hormone is reduced by at least 25%.

400. The compound of any one of paragraphs 393-398, wherein the level of adrenocorticotropic hormone is reduced by at least 40%.

401. The compound of any one of paragraphs 393-398, wherein the level of adrenocorticotropic hormone is reduced by at least 50%.

402. The compound of any one of paragraphs 393-401, wherein the level of androstenedione is reduced by at least 25%.

403. The compound of any one of paragraphs 393-401, wherein the level of androstenedione is reduced by at least 30%.

404. The compound of any one of paragraphs 393-401, wherein the level of androstenedione is reduced by at least 50%.

405. The compound of any one of paragraphs 393-401, wherein the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

406. The compound of any one of paragraphs 393-405, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

407. The compound of any one of paragraphs 393-406, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

408. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound is administered in an amount sufficient to reduce the level of androstenedione in the subject.

409. The compound of paragraph 408, wherein the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

410. The compound of paragraph 408 or 409, wherein the level of androstenedione is reduced by at least 25%.

411. The compound of paragraph 408 or 409, wherein the level of androstenedione is reduced by at least 30%.

412. The compound of paragraph 408 or 409, wherein the level of androstenedione is reduced by at least 50%.

413. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

414. The compound of paragraph 413, wherein the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

415. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

416. The compound of paragraph 415, wherein the corticosteroid is a glucocorticoid.

417. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital

adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cellmediated immunity, predisposition to infections, and reactivation of latent infections.

418. The compound of any one of paragraphs 413-417, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

419. The compound of any one of paragraphs 413-418, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

420. The compound of any one of paragraphs 413-417, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

421. The compound of any one of paragraphs 413-420, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

422. The compound of any one of paragraphs 413-421, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

423. The compound of any one of paragraphs 413-422, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

424. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;
(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and
(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

425. The compound of paragraph 424, further comprising (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i).

426. The compound of paragraph 425, further comprising (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

427. The compound of paragraph 425 or 426, wherein steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window.

428. The compound of any one of paragraphs 425-427, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m.

429. The compound of any one of paragraphs 425-427, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

430. The compound of any one of paragraphs 425-429, wherein steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

431. The compound of any one of paragraphs 425-429, wherein steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

432. The compound of any one of paragraphs 424-431, wherein step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

433. The compound of any one of paragraphs 424-432, wherein step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

434. The compound of any one of paragraphs 424-433, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

435. The compound of any one of paragraphs 424-433, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

436. The compound of any one of paragraphs 424-435, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

437. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof for use in a method of treating congenital adrenal hyperplasia (CAH), in a subject, wherein the subject is in a fed state.

438. The compound of paragraph 437, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition.

439. The compound of paragraph 438, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

440. The compound of paragraph 438 or 439, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

441. The compound of any one of paragraphs 438-440, wherein the nutritional composition is administered within

30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

442. The compound of any one of paragraphs 437-441, wherein administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, exhibits a positive food effect.

443. The compound of paragraph 442, wherein the positive food effect is measured in terms of $C_{max}$, AUC, or combinations thereof when comparing oral administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the fed and fasting states.

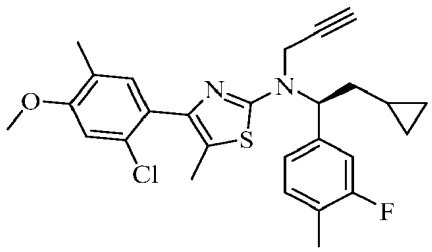
444. The compound of any one of paragraphs 437-443, wherein the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10.

445. The compound of any one of paragraphs 437-443, wherein the ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state is about 5 to about 10.

## Claims

1. A pharmaceutical composition in oral solution dosage form comprising:

   (a) a compound of Formula (I):




(I)

   or a pharmaceutically acceptable salt thereof;
   (b) one or more of a sweetener, an anti-oxidant, and a flavor; and
   (c) a liquid vehicle, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

2. The pharmaceutical composition of claim 1, comprising about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

3. The pharmaceutical composition of claim 1, comprising about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

4. The pharmaceutical composition of claim 1, comprising about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

5. The pharmaceutical composition of any one of claims 1-4, comprising a sweetener.

6. The pharmaceutical composition of any one of claims 1-5, comprising about 0.01 w/v% to about 1.5 w/v% of the sweetener.

7. The pharmaceutical composition of any one of claims 1-5, comprising about 0.1 w/v% to about 0.5 w/v% of the

sweetener.

8. The pharmaceutical composition of any one of claims 1-5, comprising about 0.15 w/v% of the sweetener.

9. The pharmaceutical composition of any one of claims 1-8, wherein the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and avantame.

10. The pharmaceutical composition of any one of claims 1-9, wherein the sweetener is saccharin.

11. The pharmaceutical composition of any one of claims 1-10, comprising an anti-oxidant.

12. The pharmaceutical composition of any one of claims 1-11, comprising about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant.

13. The pharmaceutical composition of any one of claims 1-11, comprising about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant.

14. The pharmaceutical composition of any one of claims 1-11, comprising about 0.17 w/v% of the anti-oxidant.

15. The pharmaceutical composition of any one of claims 1-14, wherein the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid.

16. The pharmaceutical composition of any one of claims 1-15, wherein the anti-oxidant is butylated hydroxytoluene.

17. The pharmaceutical composition of any one of claims 1-16, comprising a flavor.

18. The pharmaceutical composition of any one of claims 1-17, comprising about 0.01 w/v% to about 0.5 w/v% of the flavor.

19. The pharmaceutical composition of any one of claims 1-17, comprising about 0.05 w/v% to about 0.2 w/v% of the flavor.

20. The pharmaceutical composition of any one of claims 1-17, comprising about 0.10 w/v% of the flavor.

21. The pharmaceutical composition of any one of claims 1-20, wherein the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetrarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor.

22. The pharmaceutical composition of any one of claims 1-21, wherein the flavor is FONA orange flavor.

23. The pharmaceutical composition of any one of claims 1-22, comprising about 50 w/v% to about 99.9 w/v% of the liquid vehicle.

24. The pharmaceutical composition of any one of claims 1-22, comprising about 90 w/v% to about 99 w/v% of the liquid vehicle.

25. The pharmaceutical composition of any one of claims 1-22, comprising about 92 w/v% to about 97 w/v% of the liquid vehicle.

26. The pharmaceutical composition of any one of claims 1-22, comprising about 94.6 w/v% of the liquid vehicle.

27. The pharmaceutical composition of any one of claims 1-22, comprising about 70 w/v% to about 80 w/v% of the liquid vehicle.

28. The pharmaceutical composition of any one of claims 1-22, comprising about 75 w/v% of the liquid vehicle.

29. The pharmaceutical composition of any one of claims 1-28, wherein the liquid vehicle is medium-chain triglycerides.

30. The pharmaceutical composition of claim 29, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

31. The pharmaceutical composition of any one of claims 1-30, further comprising a surfactant.

32. The pharmaceutical composition of claim 31, comprising about 1 w/v% to about 50 w/v% of the surfactant.

33. The pharmaceutical composition of claim 31, comprising about 10 w/v% to about 30 w/v% of the surfactant.

34. The pharmaceutical composition of claim 31, comprising about 20 w/v% of the surfactant.

35. The pharmaceutical composition of any one of claims 31-34, wherein the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters.

36. The pharmaceutical composition of any one of claims 31-35, wherein the surfactant is oleoyl polyoxyl-6 glycerides.

37. The pharmaceutical composition of any one of claims 35-36, wherein the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

38. The pharmaceutical composition of any one of claims 1-37, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

39. The pharmaceutical composition of any one of claims 1-38, wherein the liquid vehicle is medium-chain triglycerides.

40. The pharmaceutical composition of any one of claims 1-38, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

41. The pharmaceutical composition of claim 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) a sweetener;
(c) an anti-oxidant;
(d) a flavor; and
(e) a liquid vehicle.

42. The pharmaceutical composition of claim 41, further comprising a surfactant.

43. The pharmaceutical composition of claim 1, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
(d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and
(e) about 92 w/v% to about 97 w/v% of a liquid vehicle.

44. The pharmaceutical composition of claim 1, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of a sweetener;
(c) about 0.17 w/v% of an anti-oxidant;
(d) about 0.1 w/v% of a flavor; and

(e) about 94.6 w/v% of a liquid vehicle.

**45.** The pharmaceutical composition of claim 1, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;
(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;
(d) about 0.05 w/v% to about 0.2 w/v% of a flavor;
(e) about 15 w/v% to about 25 w/v% of a surfactant; and
(f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

**46.** The pharmaceutical composition of claim 1, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of a sweetener;
(c) about 0.17 w/v% of an anti-oxidant;
(d) about 0.1 w/v% of a flavor;
(e) about 20 w/v% of a surfactant; and
(f) about 75 w/v% of a liquid vehicle.

**47.** The pharmaceutical composition of claim 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;
(b) saccharin;
(c) butylated hydroxytoluene;
(d) FONA orange flavor; and
(e) medium-chain triglycerides.

**48.** The pharmaceutical composition of claim 47, further comprising oleoyl polyoxyl-6 glycerides.

**49.** The pharmaceutical composition of claim 48, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and
(e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

**50.** The pharmaceutical composition of claim 1, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of saccharin;
(c) about 0.17 w/v% of butylated hydroxytoluene;
(d) about 0.1 w/v% of FONA orange flavor; and
(e) about 94.6 w/v% of medium-chain triglycerides.

**51.** The pharmaceutical composition of claim 1, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-

4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;
(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;
(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;
(e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and
(f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

**52.** The pharmaceutical composition of claim 1, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;
(b) about 0.15 w/v% of saccharin;
(c) about 0.17 w/v% of butylated hydroxytoluene;
(d) about 0.1 w/v% of FONA orange flavor;
(e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and
(f) about 75 w/v% of medium-chain triglycerides.

**53.** The pharmaceutical composition of claim 51 or 52, wherein:

the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS; and
the medium-chain triglycerides is Labrafac TM Lipophile WL1349.

**54.** The pharmaceutical composition of any one of claims 1-53, comprising the compound of Formula (I) as a free base.

**55.** The pharmaceutical composition of any one of claims 1-54, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base.

**56.** The pharmaceutical composition of claim 55, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base.

**57.** The pharmaceutical composition of claim 55, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg/mL, based on the weight of the free base.

**58.** The pharmaceutical composition of claim 55, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg/mL, based on the weight of the free base.

**59.** The pharmaceutical composition of any one of claims 1-58, having a viscosity between about 1 to about 50 centipoise at about 25 °C.

**60.** A method for preparing the pharmaceutical composition of any one of claims 1-59, comprising:

(a) mixing a liquid vehicle with a sweetener;
(b) mixing the mixture of step (a) with an anti-oxidant and a flavor;
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and
(d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

**61.** The method of claim 60, wherein step (a) comprises mixing a liquid vehicle with a sweetener and a surfactant.

**62.** A pharmaceutical composition of any one of claims 1-59 for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

**63.** The pharmaceutical composition for use according to claim 62, wherein the subject is in a fed state.

**64.** The pharmaceutical composition for use according to claim 62 or 63, wherein the subject is administered the phar-

maceutical composition with a nutritional composition.

**65.** The pharmaceutical composition for use according to claim 64, wherein the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%.

**66.** The pharmaceutical composition for use according to claim 64, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

**67.** The pharmaceutical composition for use according to any one of claims 64-66, wherein the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces.

**68.** The pharmaceutical composition for use according to any one of claims 64-67, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

**69.** The pharmaceutical composition for use according to any one of claims 64-68, wherein the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

**70.** The pharmaceutical composition for use according to any one of claims 63-69, wherein administering the pharmaceutical composition exhibits a positive food effect.

**71.** The pharmaceutical composition for use according to claim 70, wherein the positive food effect is measured in terms of $C_{max}$, AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.

**72.** The pharmaceutical composition for use according to any one of claims 63-71, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

**73.** The pharmaceutical composition for use according to any one of claims 63-71, wherein the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

**74.** The pharmaceutical composition for use according to any one of claims 63-71, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

**75.** The pharmaceutical composition for use according to any one of claims 63-71, wherein the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

**76.** The pharmaceutical composition for use according to any one of claims 62-75, wherein the subject is a human subject.

**77.** The pharmaceutical composition for use according to any one of claims 63-69, wherein the pharmaceutical composition exhibits a positive food effect when administered orally.

**78.** The pharmaceutical composition for use according to claim 77, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10.

**79.** The pharmaceutical composition for use according to claim 77, wherein the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 1 to about 4 or about 5 to about 10.

**80.** The pharmaceutical composition for use according to claim 77, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3.

**81.** The pharmaceutical composition for use according to claim 77, wherein the compound of Formula (I) has a ratio of the $C_{max}$ in the fed state to the $C_{max}$ in the fasted state of about 1.5 to about 3.

**82.** The pharmaceutical composition for use according to any one of claims 62-81, wherein the pharmaceutical composition is administered to the subject with a meal.

**83.** The pharmaceutical composition for use according to claim 82, wherein the meal is a high fat meal.

**84.** The pharmaceutical composition for use according to claim 82, wherein the meal is a low fat meal.

**85.** The pharmaceutical composition for use according to any one of claims 82-84, wherein the pharmaceutical composition is administered within about 5 minutes after the start of the meal.

**86.** The pharmaceutical composition for use according to any one of claims 82-85, wherein the meal is an evening meal.

**87.** The pharmaceutical composition for use according to any one of claims 82-85, wherein the meal is a morning meal.

**88.** The pharmaceutical composition for use according to any one of claims 82-87, wherein administering the pharmaceutical composition exhibits a positive food effect.

**89.** The pharmaceutical composition for use according to claim 88, wherein the positive food effect is measured in terms of $C_{max}$, AUC, or combinations thereof of the compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.

**90.** The pharmaceutical composition for use according to any one of claims 82-89, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

**91.** The pharmaceutical composition for use according to any one of claims 82-90, wherein the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

**92.** The pharmaceutical composition for use according to any one of claims 82-89, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

**93.** The pharmaceutical composition for use according to any one of claims 82-89 and 92, wherein the ratio of the $C_{max}$ of the compound of Formula (I) in the fed state to the $C_{max}$ of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

**94.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**95.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**96.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**97.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**98.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**99.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises

administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**100.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**101.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**102.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**103.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**104.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**105.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**106.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**107.** The pharmaceutical composition for use according to any one of claims 62-93, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

**108.** The pharmaceutical composition for use according to any one of claims 62-107, wherein the subject is concurrently receiving a dose of a glucocorticoid.

**109.** The pharmaceutical composition for use according to claim 108, wherein the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate.

**110.** The pharmaceutical composition for use according to claim 108 or 109, wherein the glucocorticoid is cortisol (hydrocortisone).

**111.** The pharmaceutical composition for use according to claim 108 or 109, wherein the glucocorticoid is cortisone.

**112.** The pharmaceutical composition for use according to claim 108 or 109, wherein the glucocorticoid is prednisone.

**113.** The pharmaceutical composition for use according to any one of claims 108-112, wherein the glucocorticoid dose is measured in hydrocortisone equivalents.

**114.** The pharmaceutical composition for use according to any one of claims 108-113, wherein the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents.

**115.** The pharmaceutical composition for use according to any one of claims 108-114, wherein the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition.

**116.** The pharmaceutical composition for use according to any one of claims 108-114, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m$^2$/day as measured after a time period of administration of the pharmaceutical composition.

**117.** The pharmaceutical composition for use according to any one of claims 108-114, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m$^2$/day as measured after a time period of administration of the pharmaceutical composition.

**118.** The pharmaceutical composition for use according to any one of claims 108-114, wherein the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m$^2$/day as measured after a time period of administration of the pharmaceutical composition.

**119.** The pharmaceutical composition for use according to any one of claims 108-118, wherein the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition

**120.** The pharmaceutical composition for use according to any one of claims 108-118, wherein the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

**121.** The pharmaceutical composition for use according to any one of claims 108-118, wherein the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

**122.** The pharmaceutical composition for use according to any one of claims 108-118, wherein the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

**123.** The pharmaceutical composition for use according to any one of claims 108-118, wherein the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

**124.** The pharmaceutical composition for use according to any one of claims 108-118, wherein the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

**125.** The pharmaceutical composition for use according to any one of claims 108-118, wherein the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

**126.** The pharmaceutical composition for use according to any one of claims 108-118, wherein the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

**127.** The pharmaceutical composition for use according to any one of claims 108-118, wherein the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

**128.** The pharmaceutical composition for use according to any one of claims 108-118, wherein the glucocorticoid dose

of the subject is reduced by greater than about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

**129.** The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.

**130.** The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.

**131.** The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

**132.** The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition.

**133.** The pharmaceutical composition for use according to any one of claims 62-132, wherein the level of adrenocorticotropic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

**134.** The pharmaceutical composition for use according to any one of claims 62-132, wherein the level of adrenocorticotropic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

**135.** The pharmaceutical composition for use according to any one of claims 62-132, wherein the level of adrenocorticotropic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

**136.** The pharmaceutical composition for use according to any one of claims 62-132, wherein the level of adrenocorticotropic hormone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

**137.** The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the pharmaceutical composition.

**138.** The pharmaceutical composition for use according to any one of claims 62-137, wherein the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

**139.** The pharmaceutical composition for use according to any one of claims 62-137, wherein the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

**140.** The pharmaceutical composition for use according to any one of claims 62-137, wherein the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

**141.** The pharmaceutical composition for use according to any one of claims 62-137, wherein the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

**142.** The pharmaceutical composition for use according to any one of claims 62-137, wherein the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

**143.** The pharmaceutical composition for use according to any one of claims 62-142, wherein the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

**144.** The pharmaceutical composition for use according to any one of claims 62-142, wherein the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

**145.** The pharmaceutical composition for use according to any one of claims 62-142, wherein the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

**146.** The pharmaceutical composition for use according to any one of claims 62-142, wherein the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

**147.** The pharmaceutical composition for use according to any one of claims 62-142, wherein the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**148.** The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition.

**149.** The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

**150.** The pharmaceutical composition for use according to any one of claims 62-128, wherein the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

**151.** The pharmaceutical composition for use according to any one of claims 108-150, wherein the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition.

**152.** The pharmaceutical composition for use according to claim 151, wherein one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition.

**153.** The pharmaceutical composition for use according to any one of claims 115-152, wherein the time period of administration is at least about 4 weeks.

**154.** The pharmaceutical composition for use according to any one of claims 115-152, wherein the time period of administration is at least about 24 weeks.

**155.** The pharmaceutical composition for use according to any one of claims 115-152, wherein the time period of administration is at least about one year.

**156.** The pharmaceutical composition for use according to any one of claims 62-155, wherein the subject is a pediatric subject.

**157.** The pharmaceutical composition for use according to claim 156, wherein the pediatric subject is less than or equal to six years old.

**158.** The pharmaceutical composition for use according to claim 156, wherein the pediatric subject is greater than six years old and less than eleven years old.

**159.** The pharmaceutical composition for use according to claim 156, wherein the pediatric subject is greater than ten years old and less than fifteen years old.

**160.** The pharmaceutical composition for use according to claim 156, wherein the pediatric subject is greater than fourteen years old and less than nineteen years old.

**161.** The pharmaceutical composition for use according to any one of claims 62-155, wherein the subject is an adult subject.

**162.** The pharmaceutical composition for use according to any one of claims 161, wherein the adult subject is over eighteen years old.

**163.** The pharmaceutical composition for use according to any one of claims 62-162, wherein the subject is female.

**164.** The pharmaceutical composition for use according to any one of claims 62-162, wherein the subject is male.

**165.** The pharmaceutical composition for use according to any one of claims 62-164, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

**166.** The pharmaceutical composition for use according to any one of claims 62-164, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid crystalline salt.

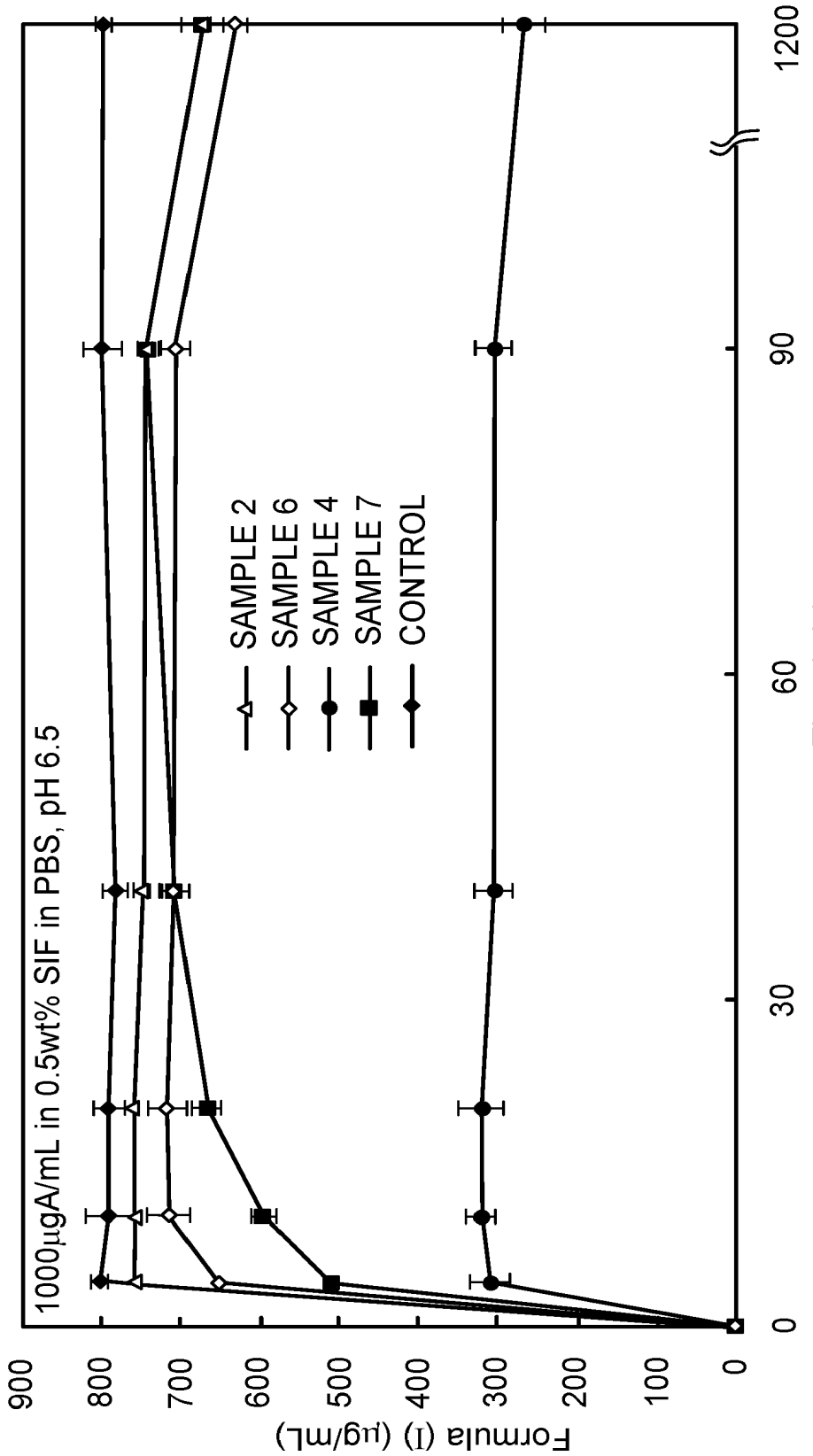

1000μgA/mL in 0.5wt% SIF in PBS, pH 6.5
SAMPLE 2
SAMPLE 6
SAMPLE 4
SAMPLE 7
CONTROL
Formula (I) (μg/mL)
Time (min)
0
100
200
300
400
500
600
700
800
900
0
30
60
90
1200

FIG. 1

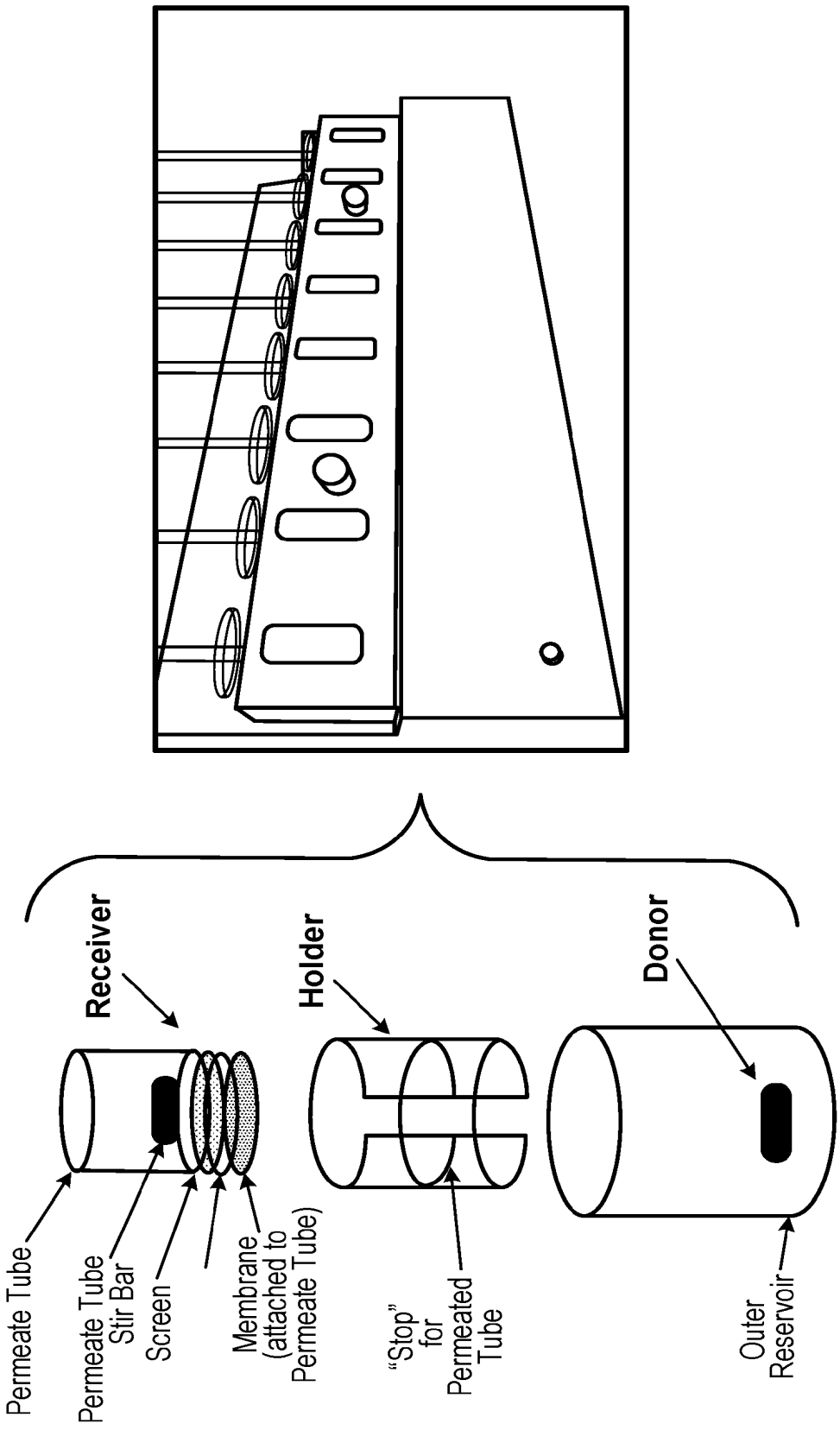

Receiver
Holder
Donor
Permeate Tube
Permeate Tube Stir Bar
Screen
Membrane (attached to Permeate Tube)
"Stop" for Permeated Tube
Outer Reservoir

FIG. 2

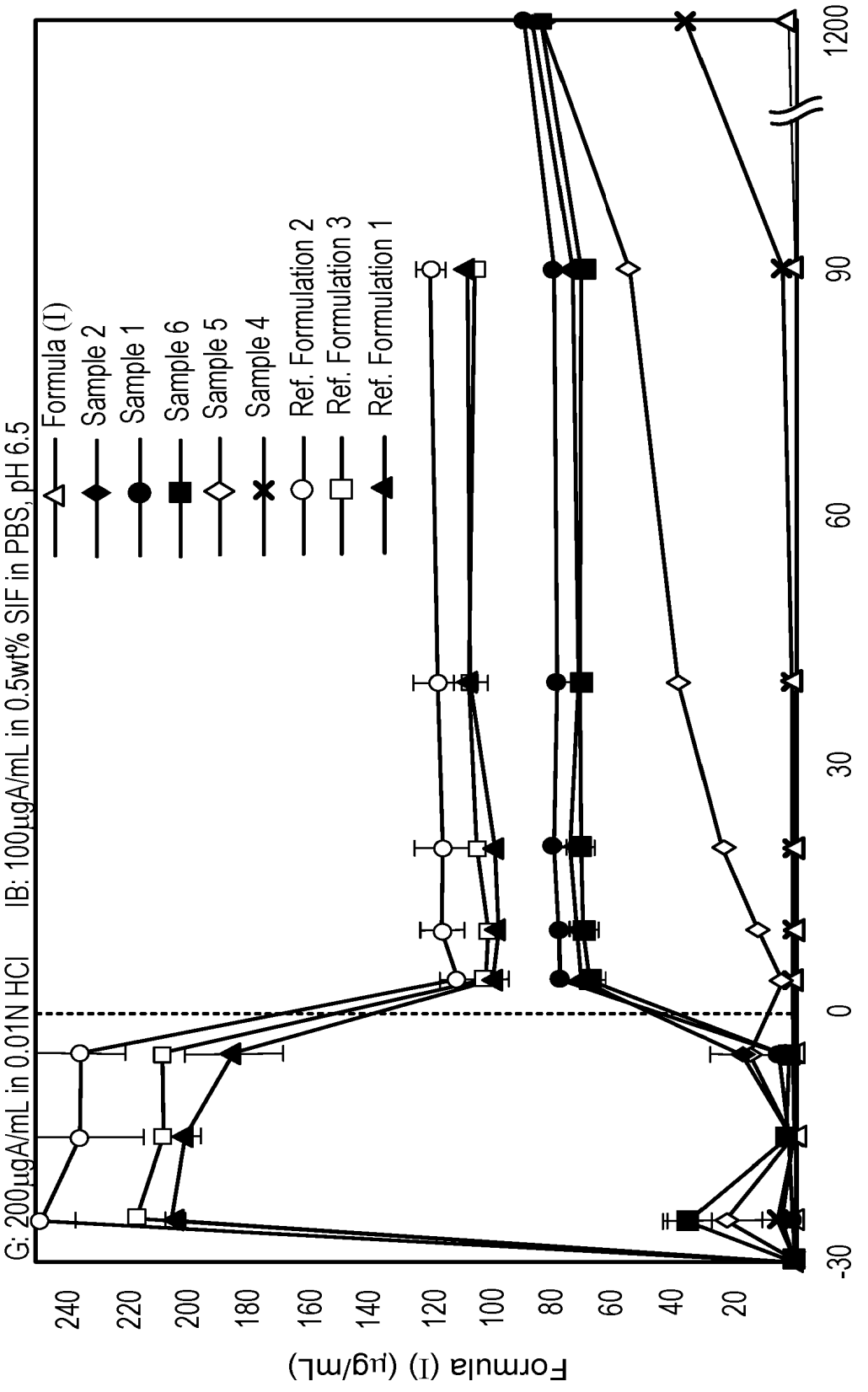

G: 200μgA/mL in 0.01N HCl IB: 100μgA/mL in 0.5wt% SIF in PBS, pH 6.5
Formula (I)
Sample 2
Sample 1
Sample 6
Sample 5
Sample 4
Ref. Formulation 2
Ref. Formulation 3
Ref. Formulation 1
Formula (I) (μg/mL)
240
220
200
180
160
140
120
100
80
60
40
20
-30
0
30
60
90
1200
Time (min)

FIG. 3

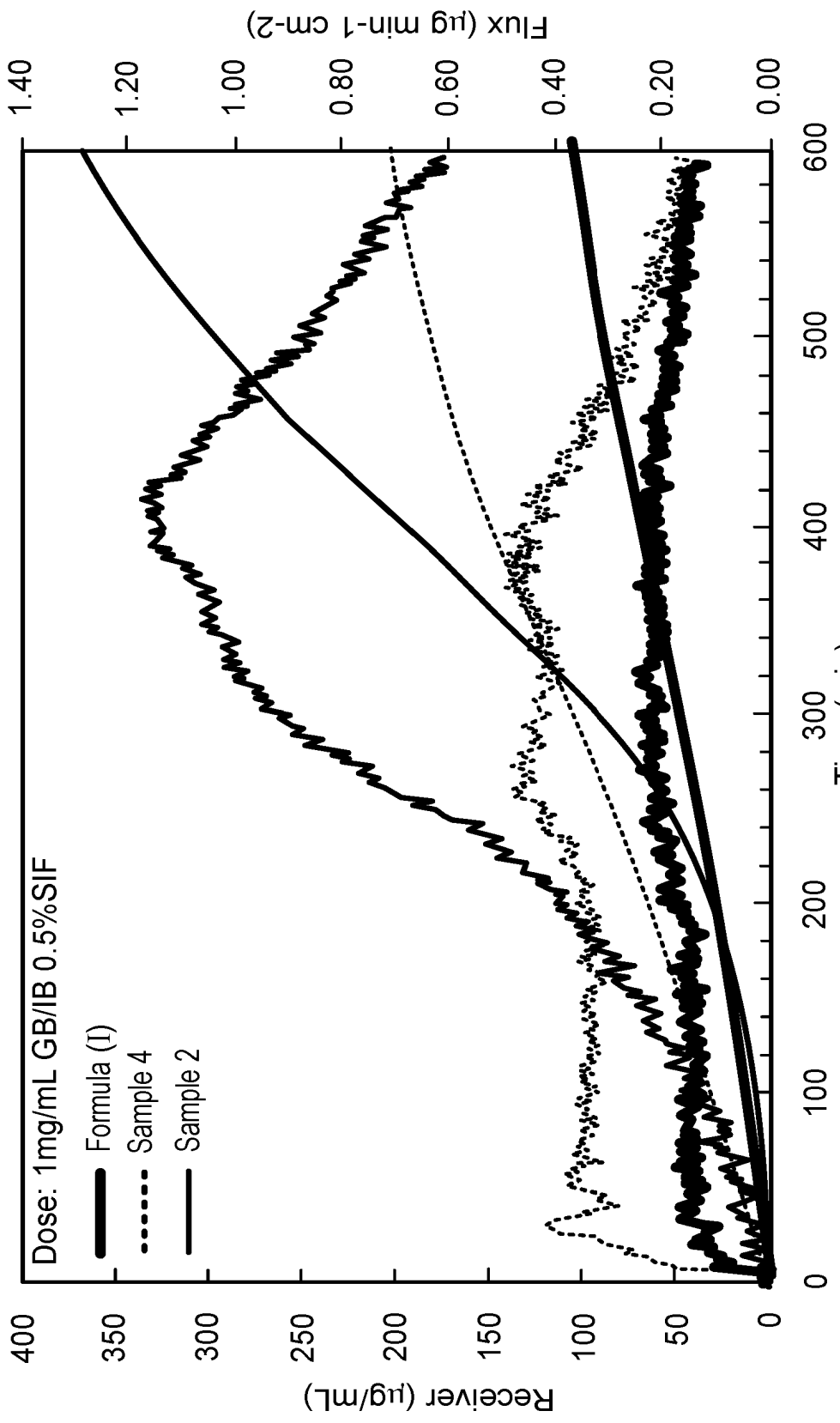

Dose: 1mg/mL GB/IB 0.5%SIF
Formula (I)
Sample 4
Sample 2
Receiver (µg/mL)
Flux (µg min-1 cm-2)
Time (min)
0
50
100
150
200
250
300
350
400
0.00
0.20
0.40
0.60
0.80
1.00
1.20
1.40
0
100
200
300
400
500
600

FIG. 4

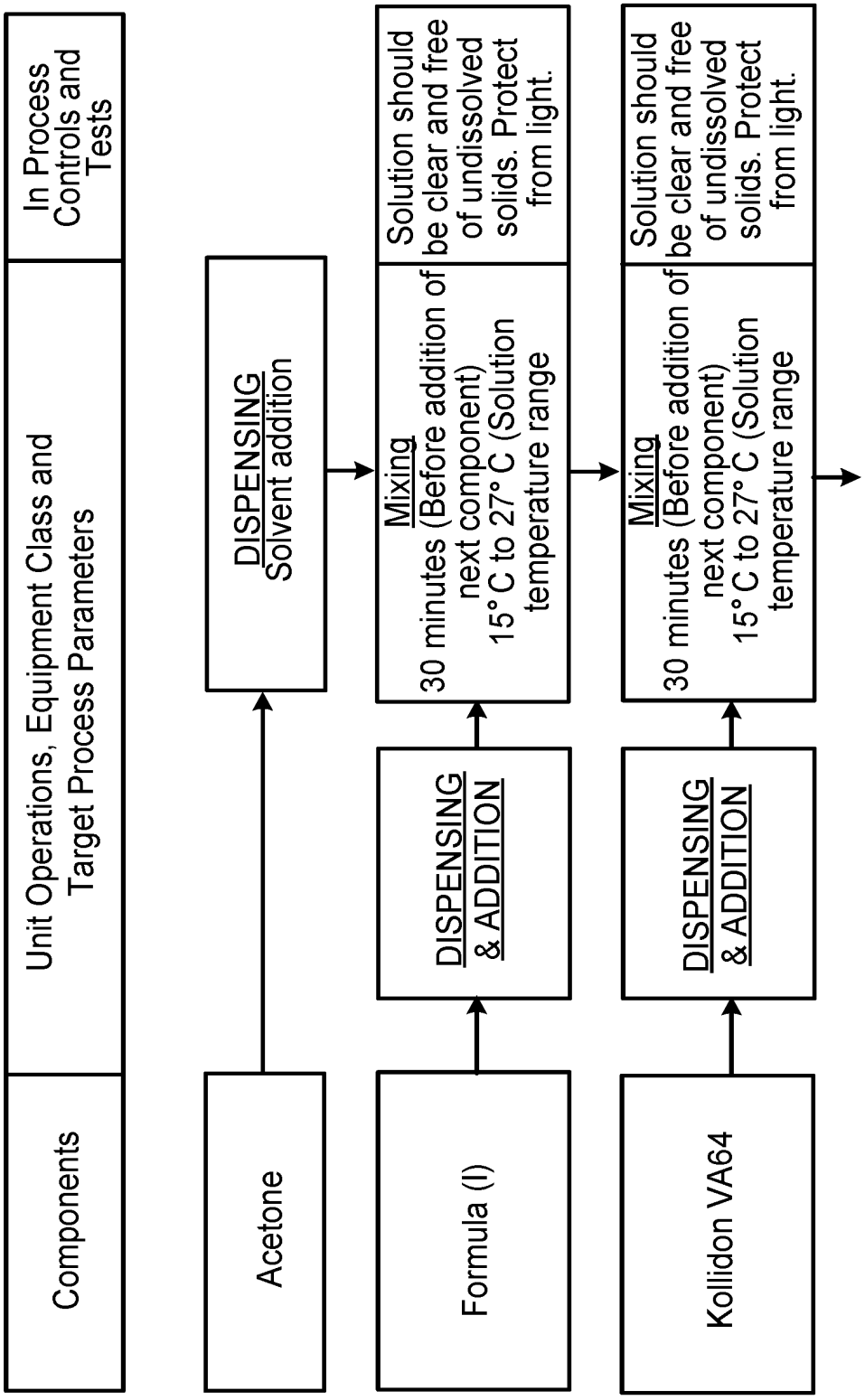

Components
Unit Operations, Equipment Class and Target Process Parameters
In Process Controls and Tests
Acetone
DISPENSING
Solvent addition
Formula (I)
DISPENSING
& ADDITION
Mixing
30 minutes (Before addition of next component)
15° C to 27° C (Solution temperature range
Solution should be clear and free of undissolved solids. Protect from light.
Kollidon VA64
DISPENSING
& ADDITION
Mixing
30 minutes (Before addition of next component)
15° C to 27° C (Solution temperature range
Solution should be clear and free of undissolved solids. Protect from light.

FIG. 5

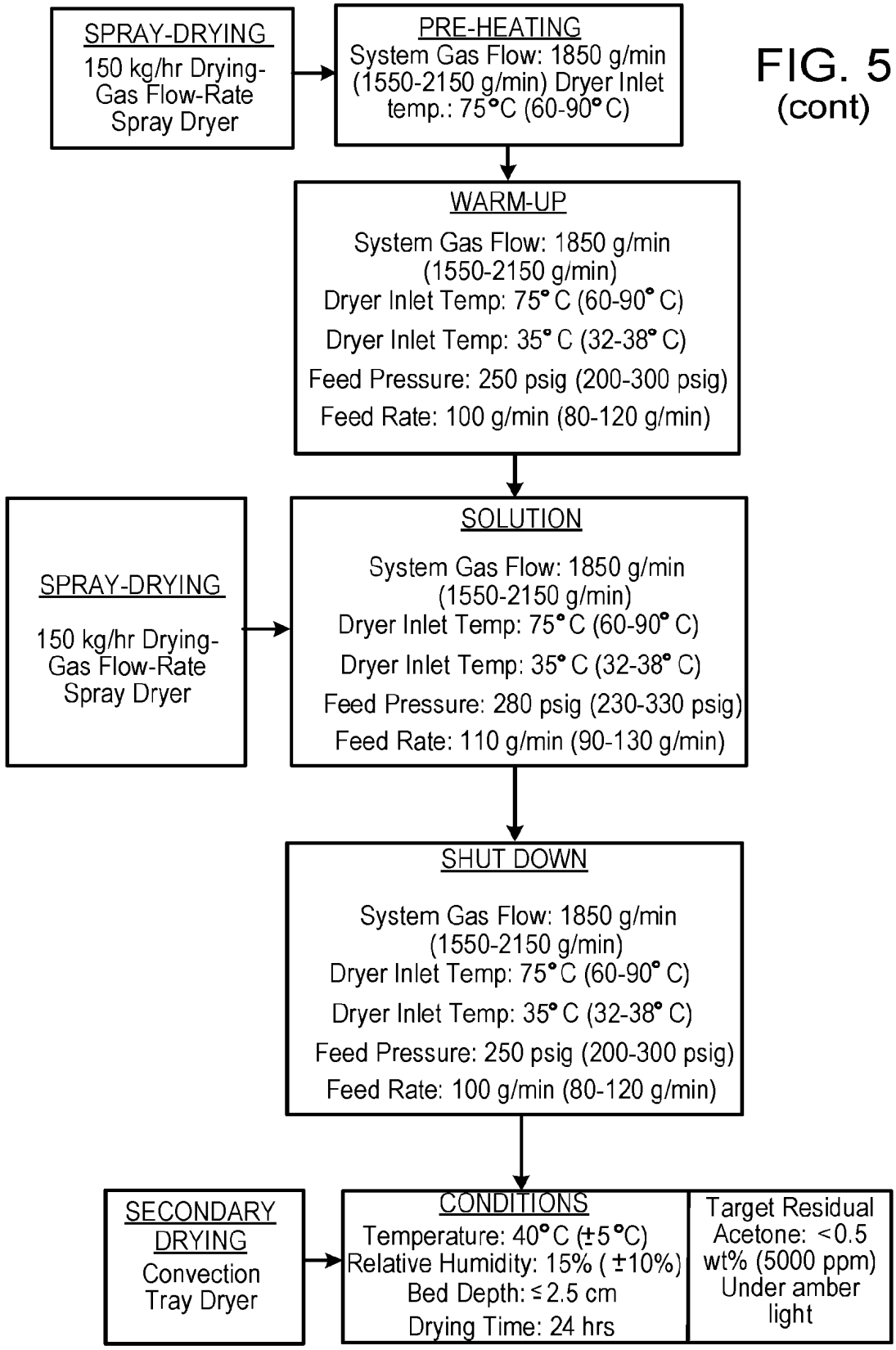

SPRAY-DRYING
150 kg/hr Drying-Gas Flow-Rate Spray Dryer
PRE-HEATING
System Gas Flow: 1850 g/min (1550-2150 g/min) Dryer Inlet temp.: 75°C (60-90°C)
WARM-UP
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 250 psig (200-300 psig)
Feed Rate: 100 g/min (80-120 g/min)
SPRAY-DRYING
150 kg/hr Drying-Gas Flow-Rate Spray Dryer
SOLUTION
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 280 psig (230-330 psig)
Feed Rate: 110 g/min (90-130 g/min)
SHUT DOWN
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 250 psig (200-300 psig)
Feed Rate: 100 g/min (80-120 g/min)
SECONDARY DRYING
Convection Tray Dryer
CONDITIONS
Temperature: 40°C (±5°C)
Relative Humidity: 15% (±10%)
Bed Depth: ≤ 2.5 cm
Drying Time: 24 hrs
Target Residual Acetone: <0.5 wt% (5000 ppm) Under amber light

FIG. 5
(cont)

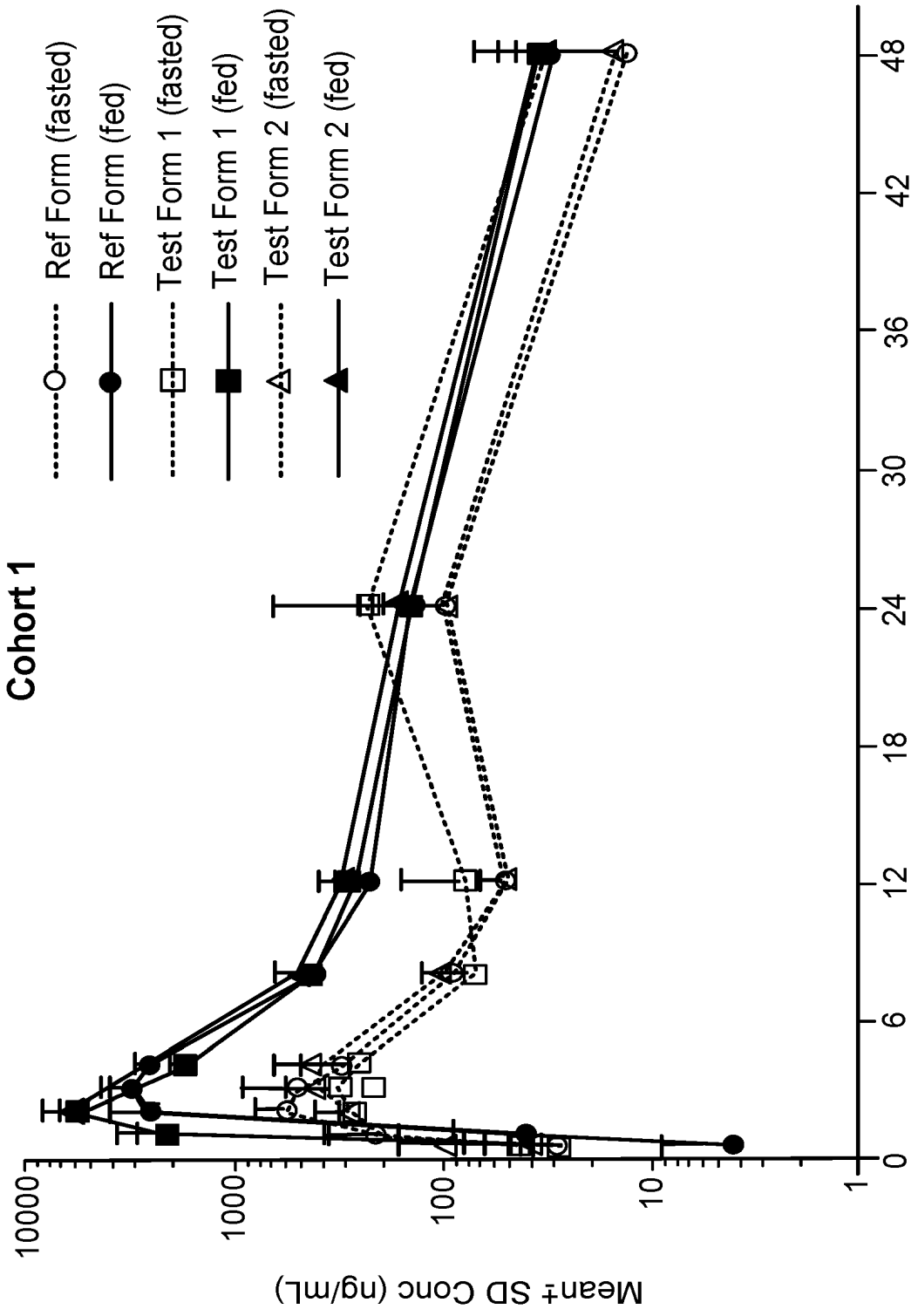

Cohort 1
Ref Form (fasted)
Ref Form (fed)
Test Form 1 (fasted)
Test Form 1 (fed)
Test Form 2 (fasted)
Test Form 2 (fed)
Mean± SD Conc (ng/mL)
10000
1000
100
10
1
0
6
12
18
24
30
36
42
48
Time (hr)

FIG. 6A

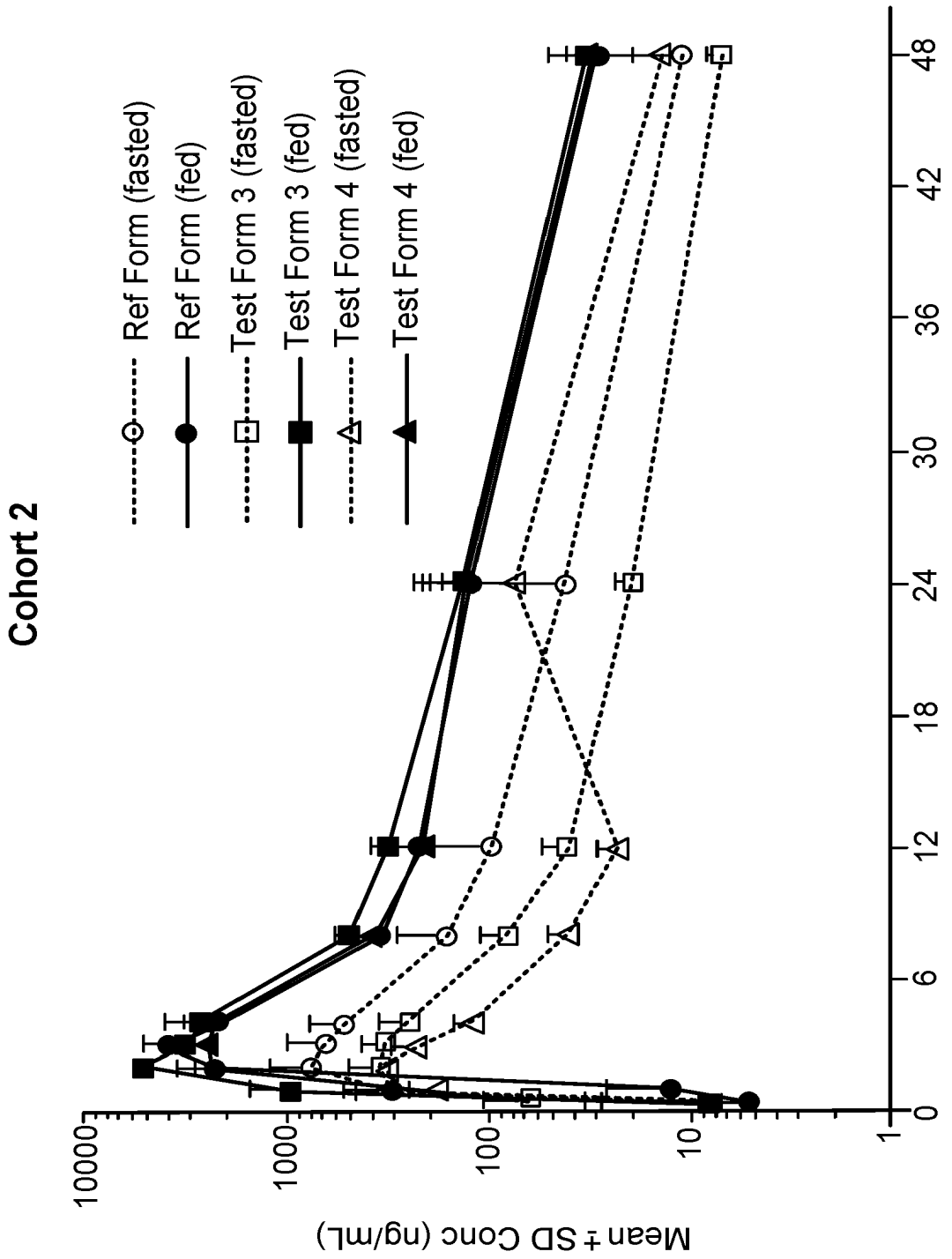

Cohort 2
Ref Form (fasted)
Ref Form (fed)
Test Form 3 (fasted)
Test Form 3 (fed)
Test Form 4 (fasted)
Test Form 4 (fed)
Mean ± SD Conc (ng/mL)
10000
1000
100
10
1
0
6
12
18
24
30
36
42
48
Time (hr)

FIG. 6B

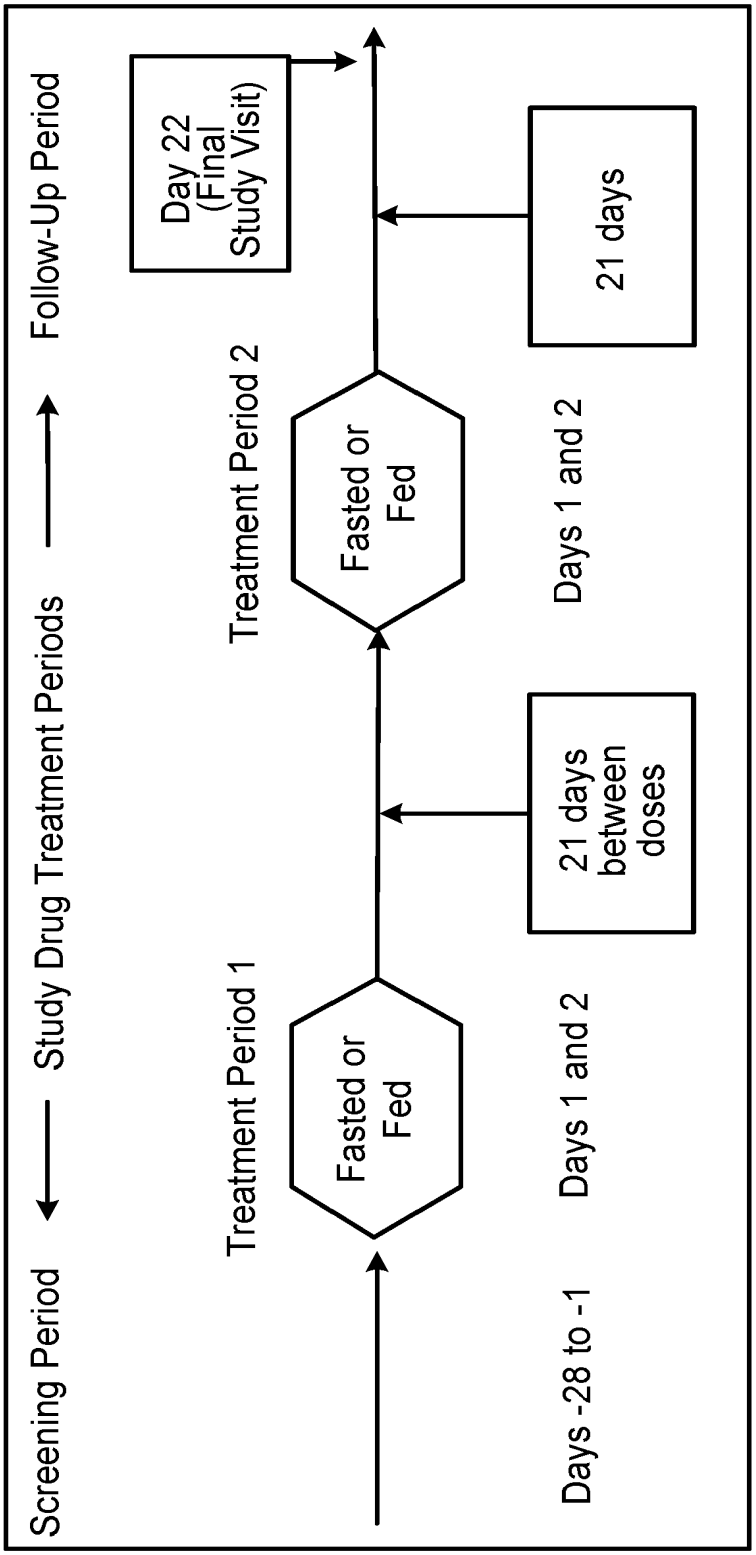

Screening Period
Study Drug Treatment Periods
Follow-Up Period
Days -28 to -1
Treatment Period 1
Fasted or Fed
Days 1 and 2
21 days between doses
Treatment Period 2
Fasted or Fed
Days 1 and 2
21 days
Day 22 (Final Study Visit)

FIG. 7

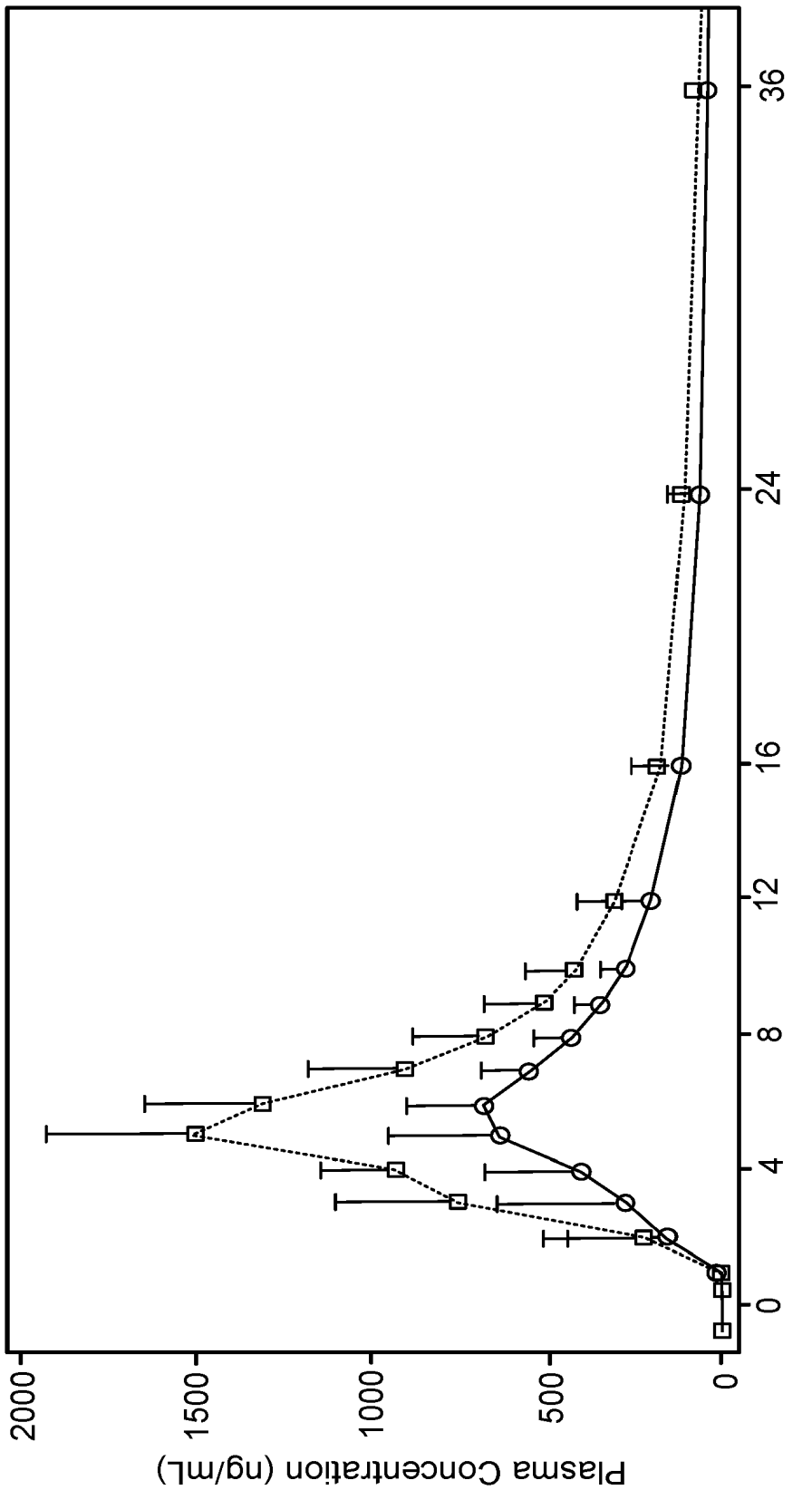

Plasma Concentration (ng/mL)
2000
1500
1000
500
0
0
4
8
12
16
24
36
Scheduled Time Postdose (Hours)
Treatment Fasted Fed

FIG. 8A

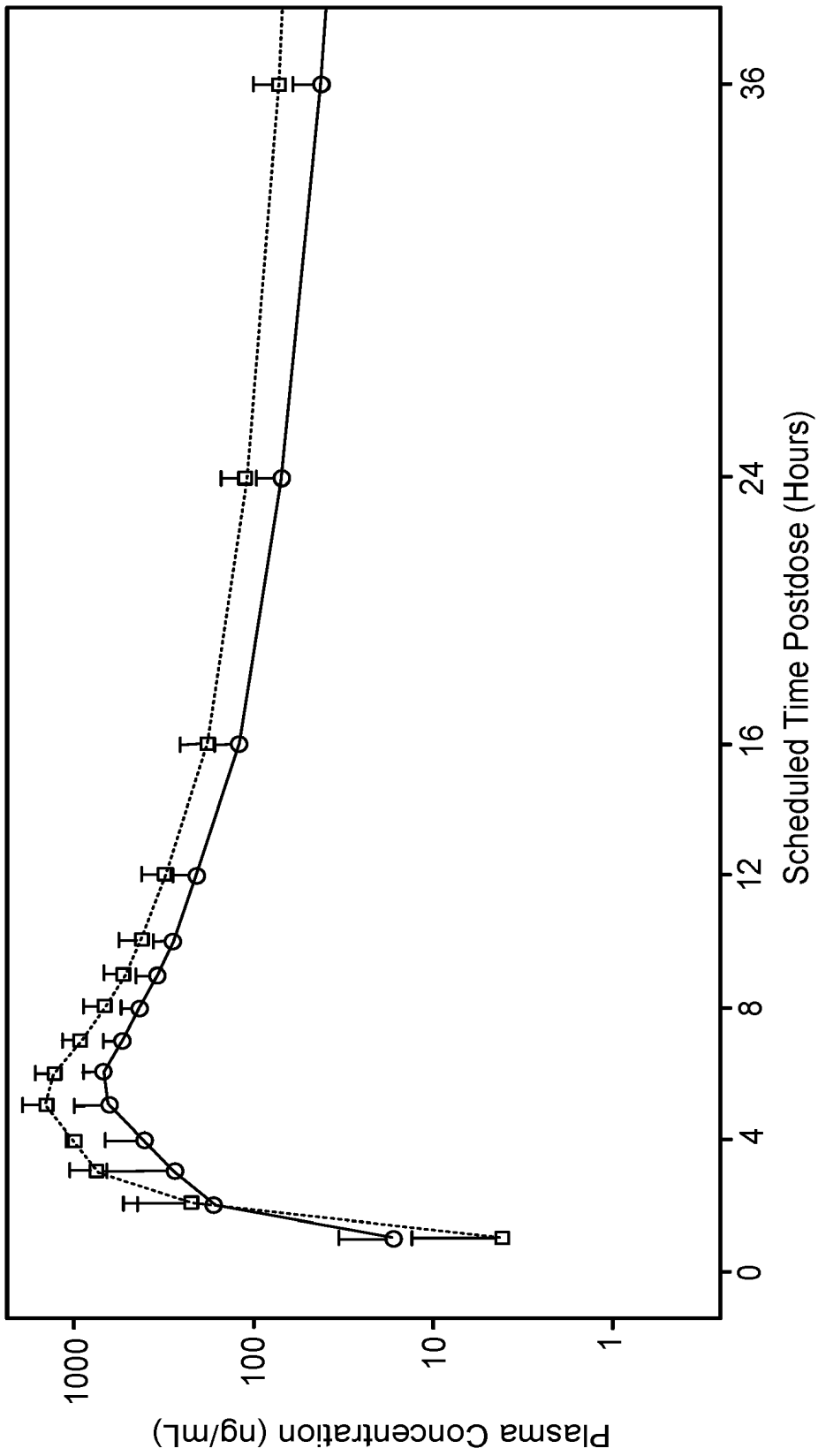

Plasma Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
24
36
Scheduled Time Postdose (Hours)
Treatment Fasted Fed

FIG. 8B

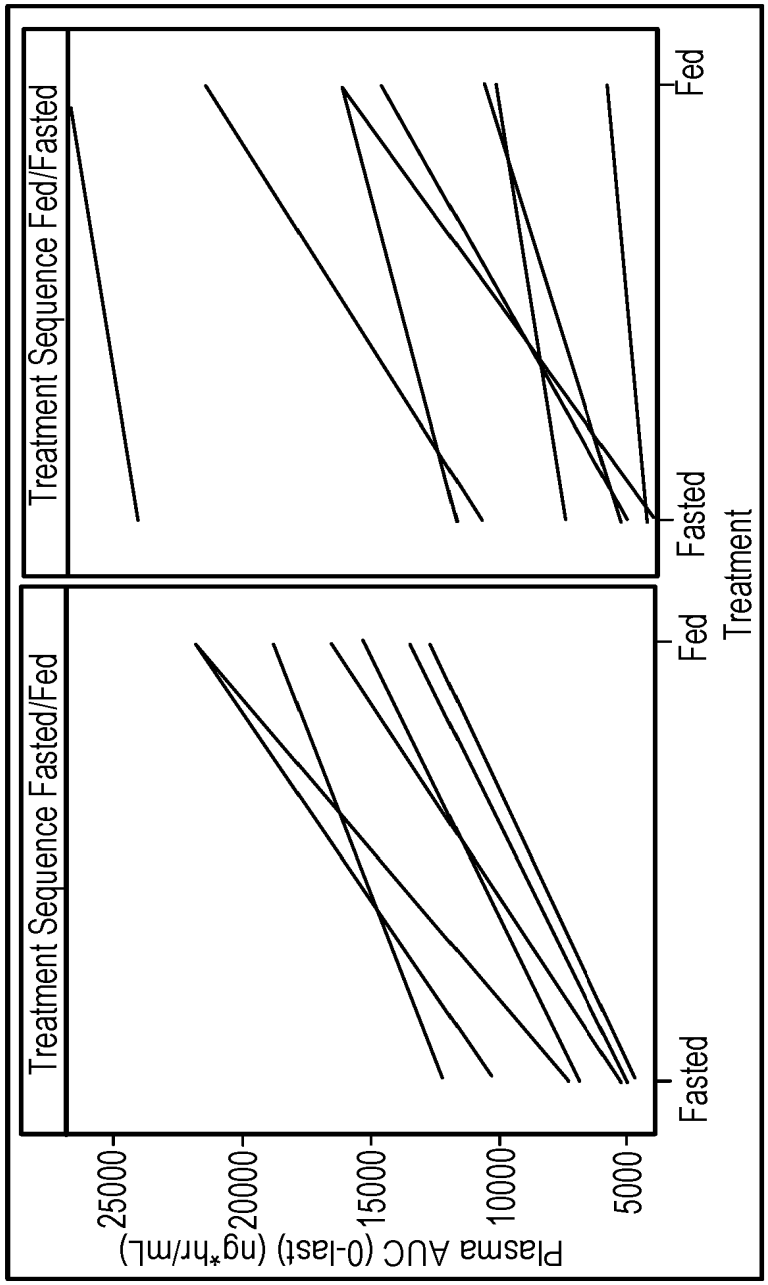

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma AUC (0-last) (ng*hr/mL)
25000
20000
15000
10000
5000
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9A

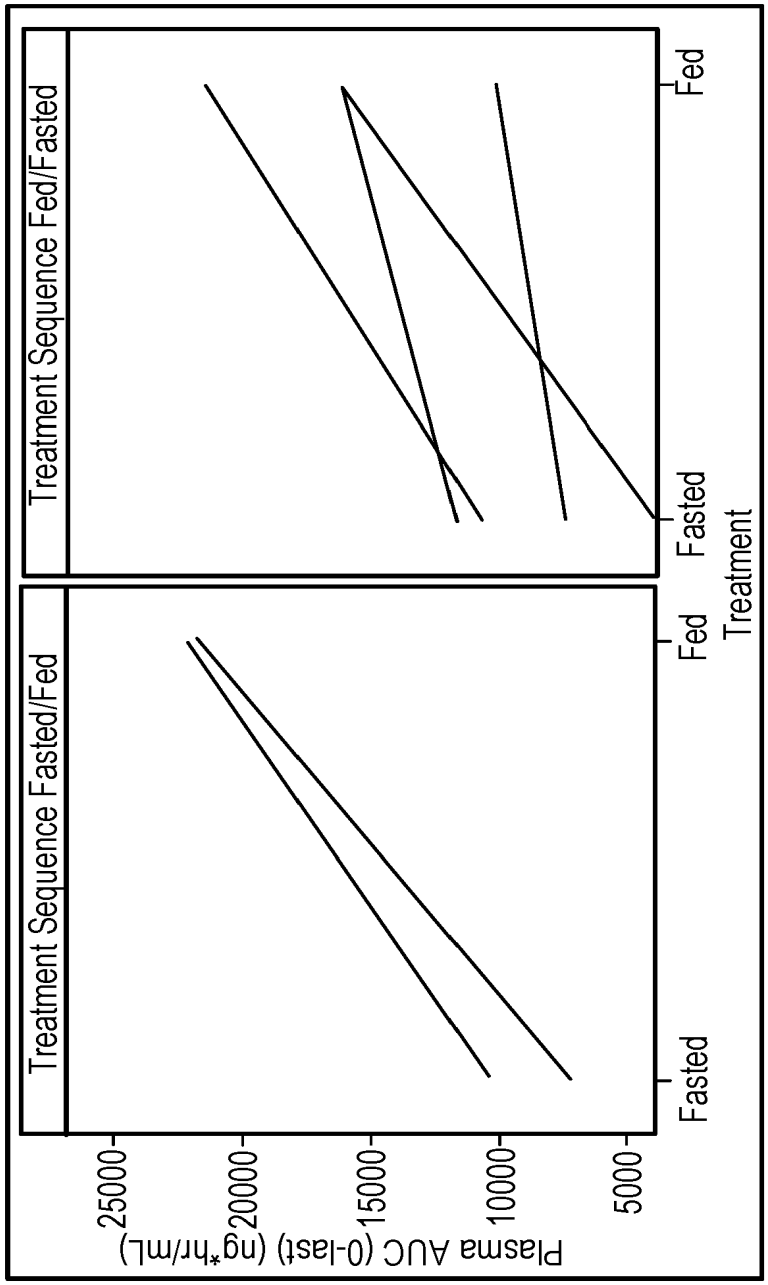

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma AUC (0-last) (ng*hr/mL)
25000
20000
15000
10000
5000
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9B

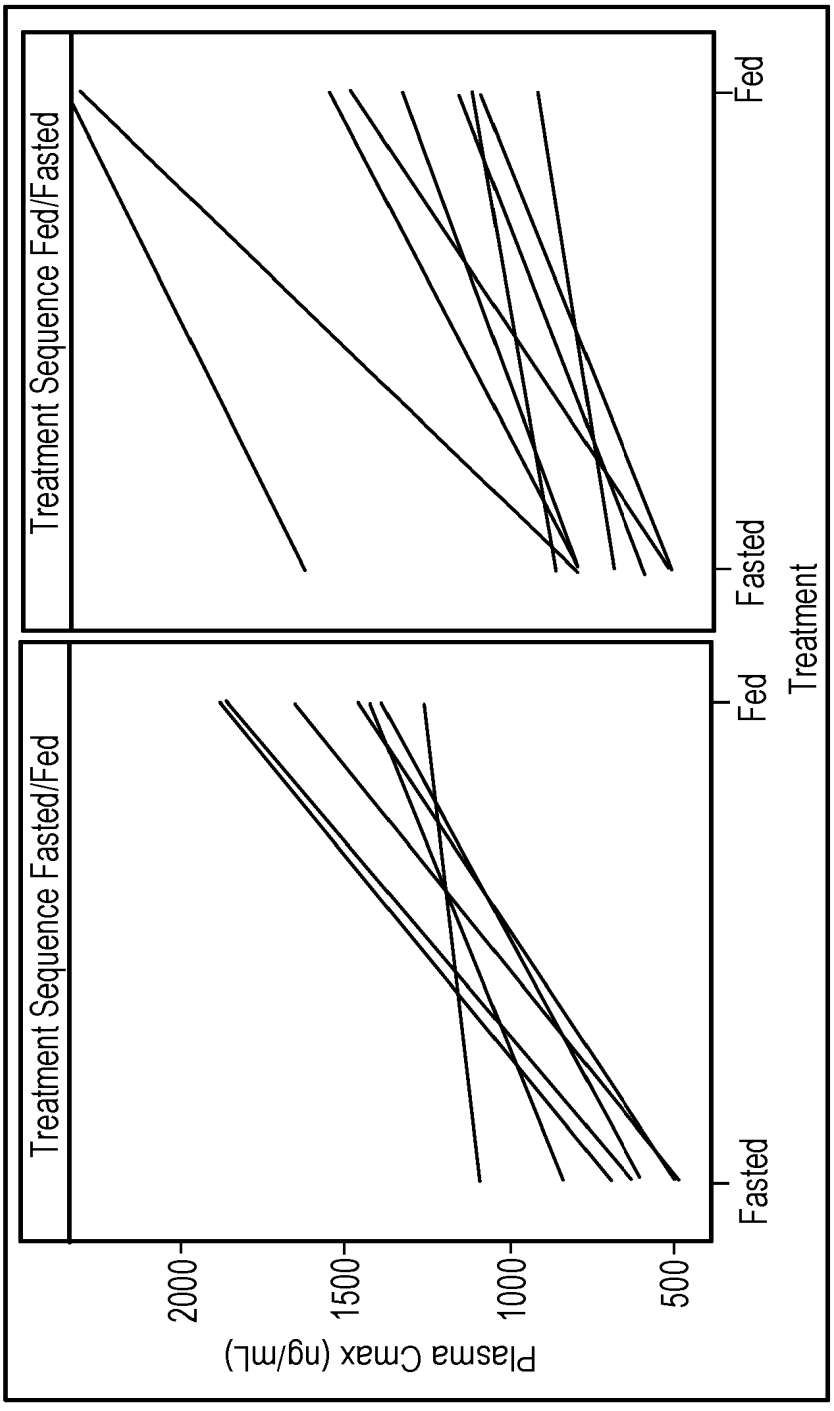
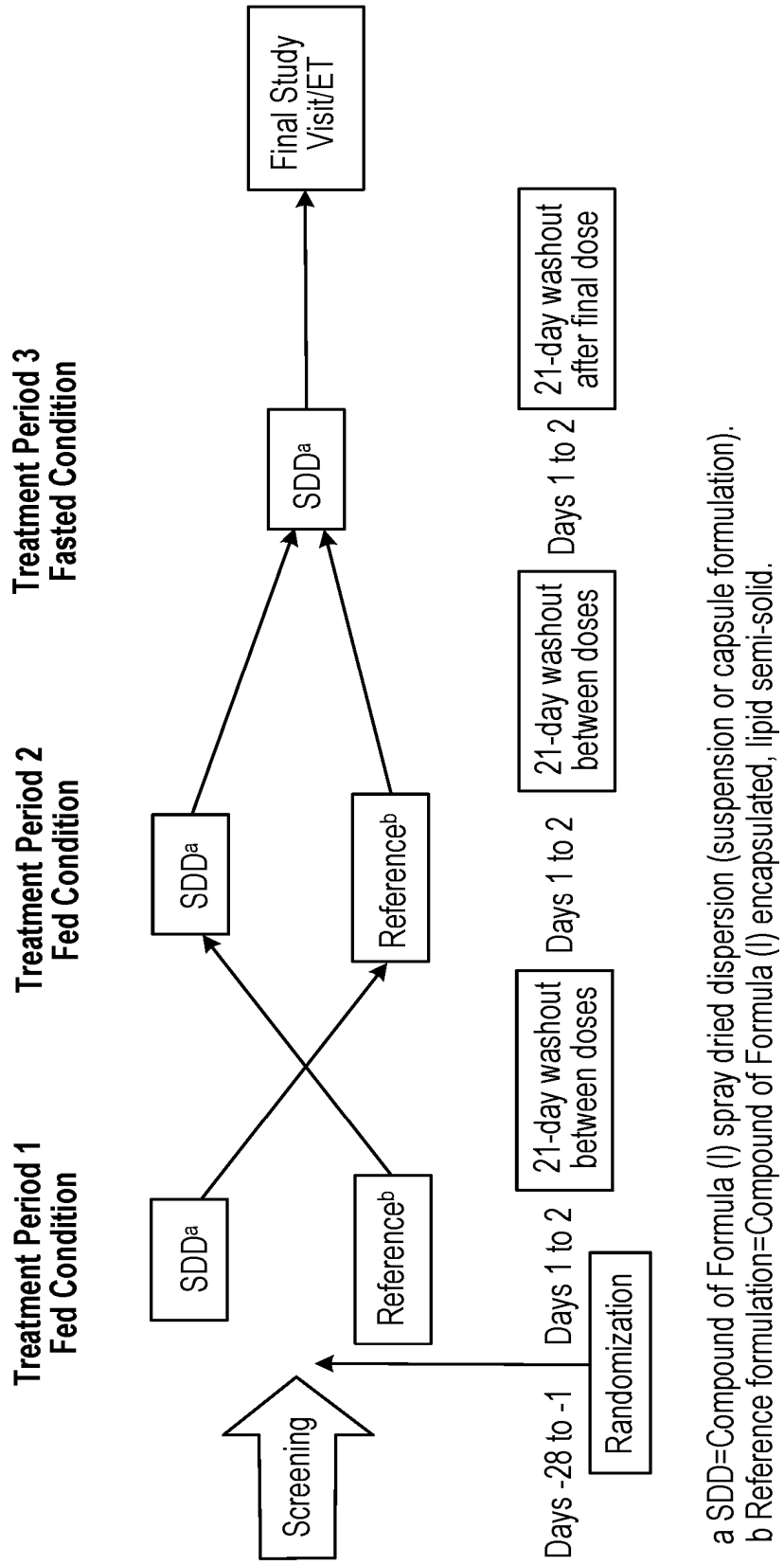

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma Cmax (ng/mL)
2000
1500
1000
500
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9C




a SDD=Compound of Formula (I) spray dried dispersion (suspension or capsule formulation).
b Reference formulation=Compound of Formula (I) encapsulated, lipid semi-solid.

FIG. 10

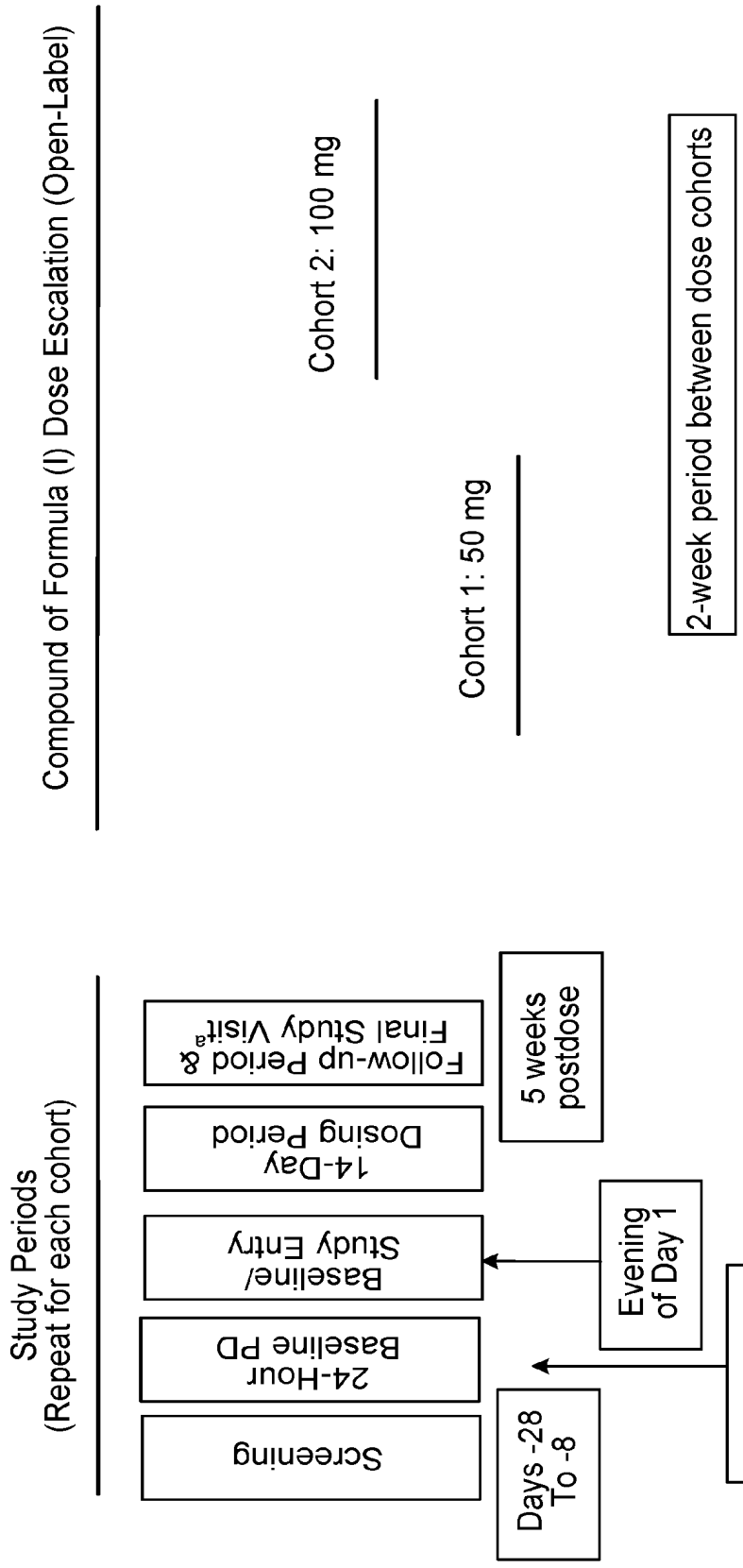



FIG. 11

a Visit on Days 21 (+3 days), 28 (+3 days), and 35 (+3 days); final study visit on Day 49 (+7 days) or early termination.
PD = pharmacodynamic.

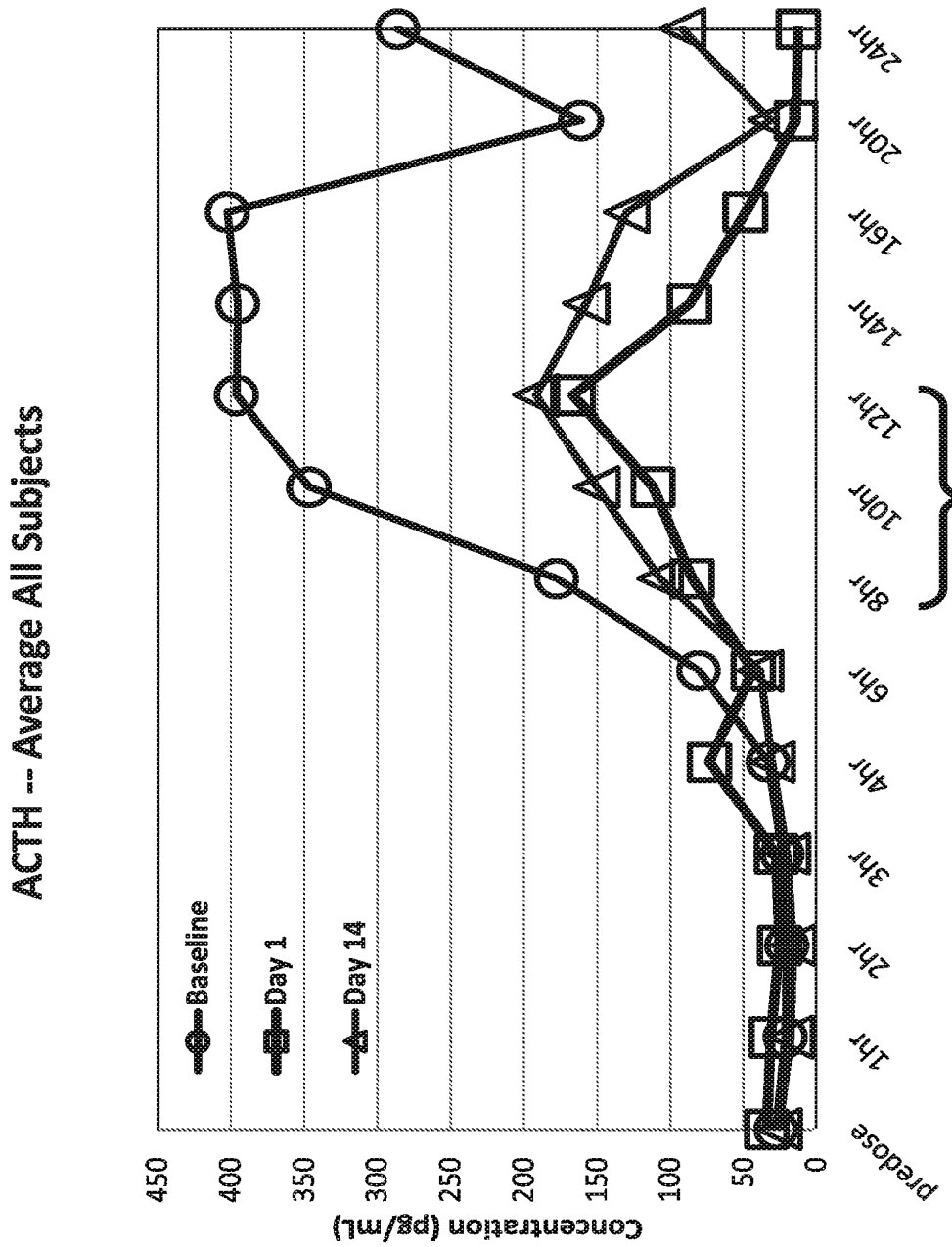

ACTH -- Average All Subjects
Concentration (pg/mL)
450
400
350
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Baseline
Day 1
Day 14
Morning
Window
6 – 10 AM

FIG. 12A

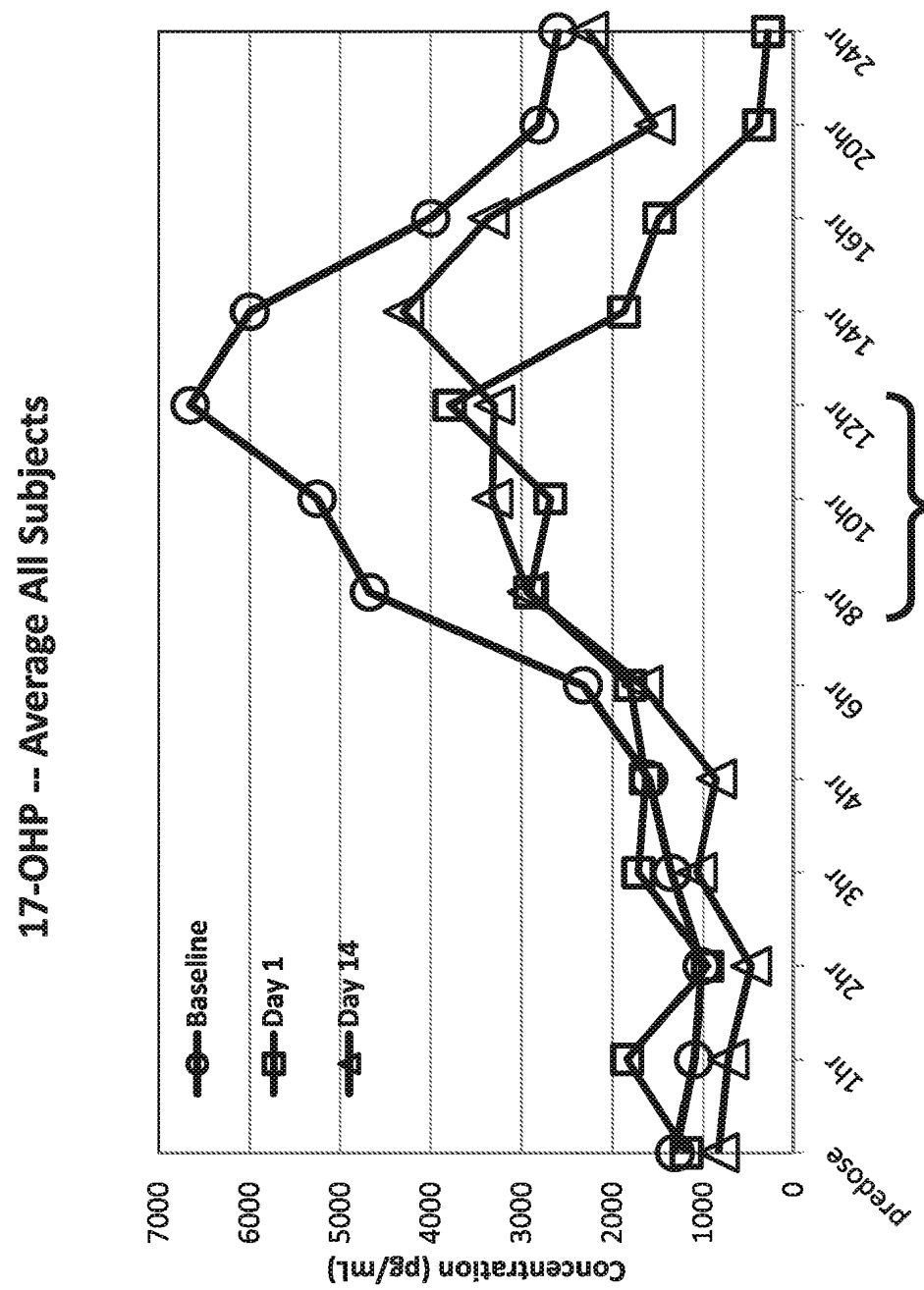

17-OHP -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 12B

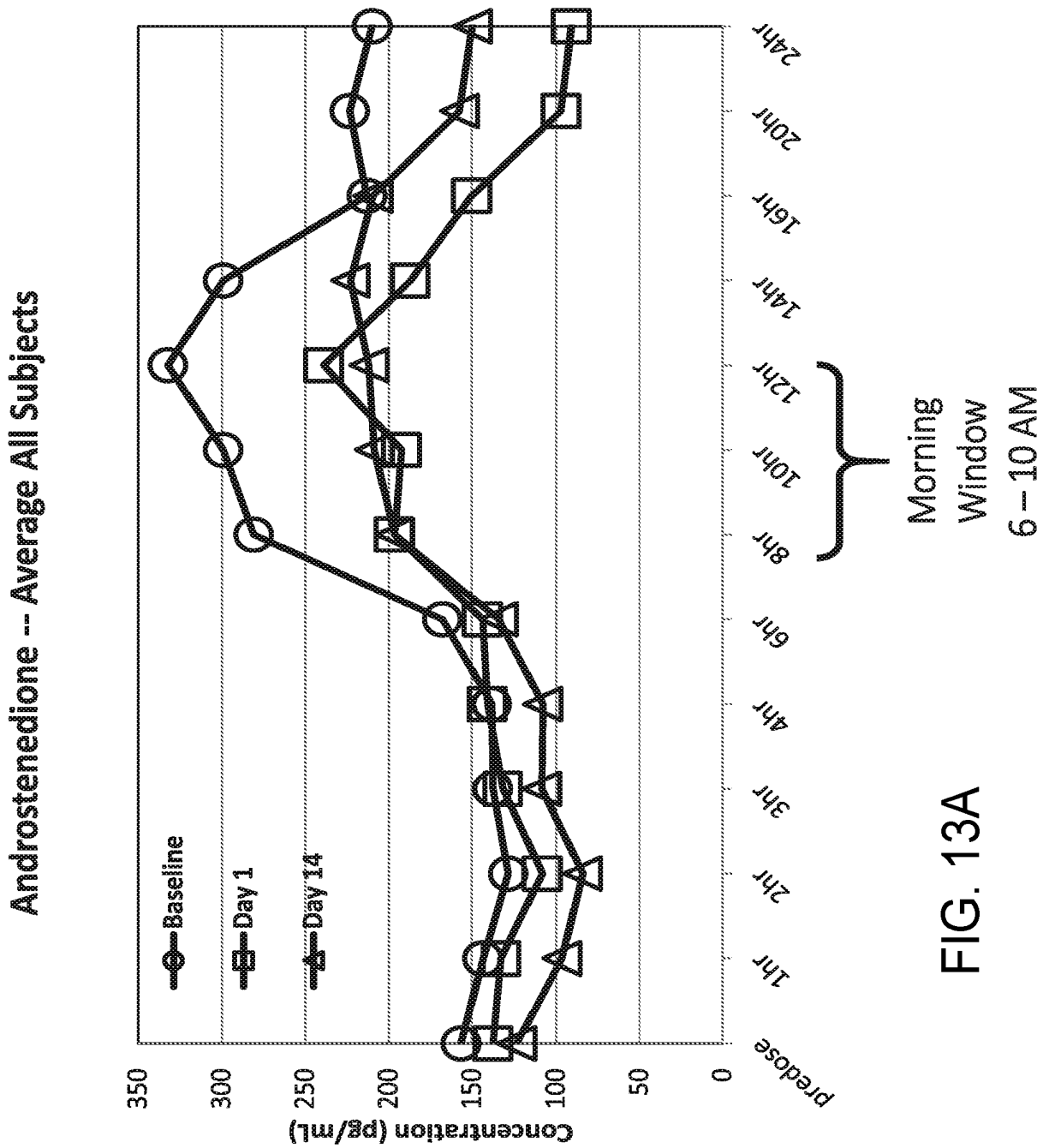

Androstenedione -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
350
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 13A

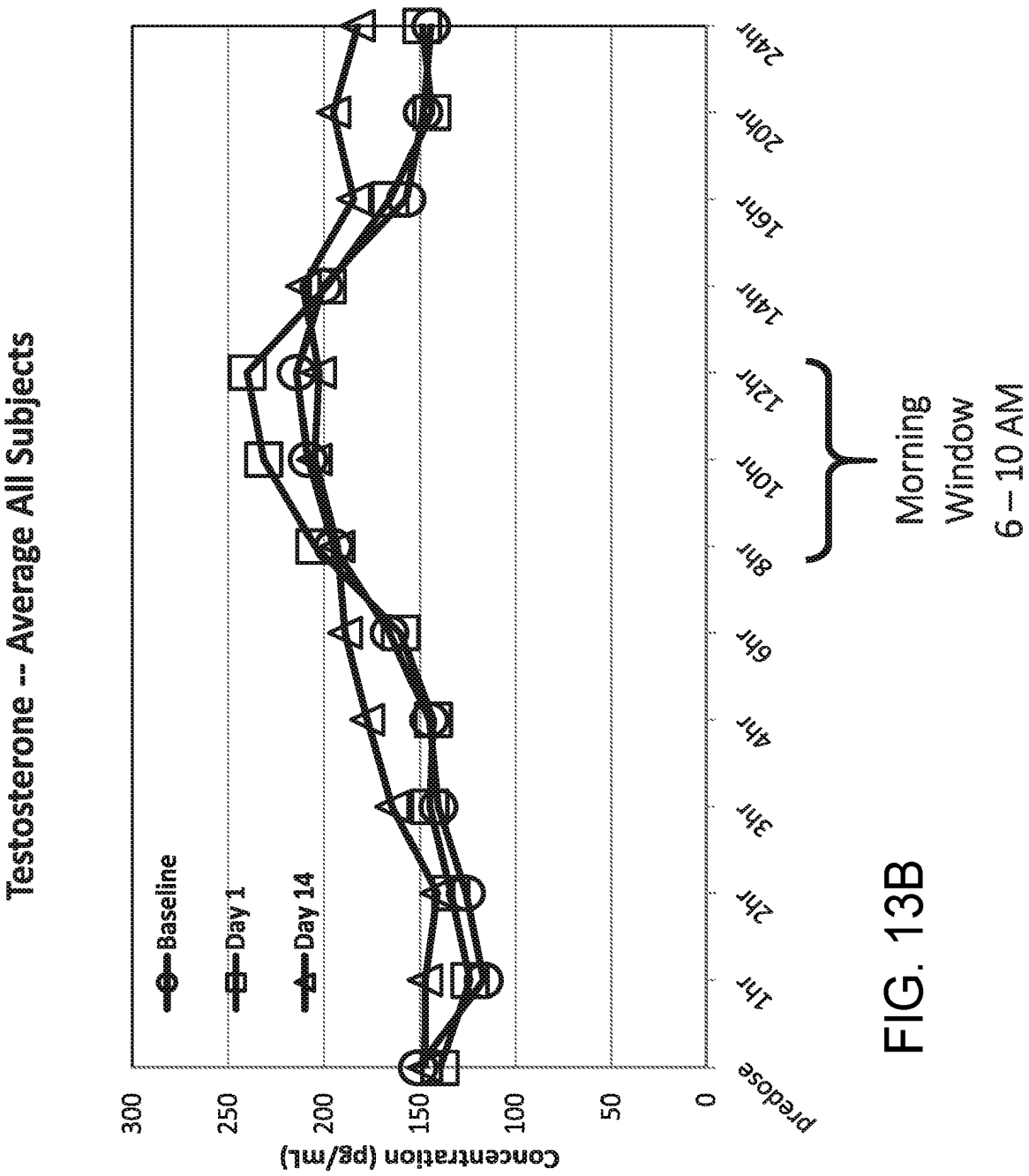

Testosterone -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 13B

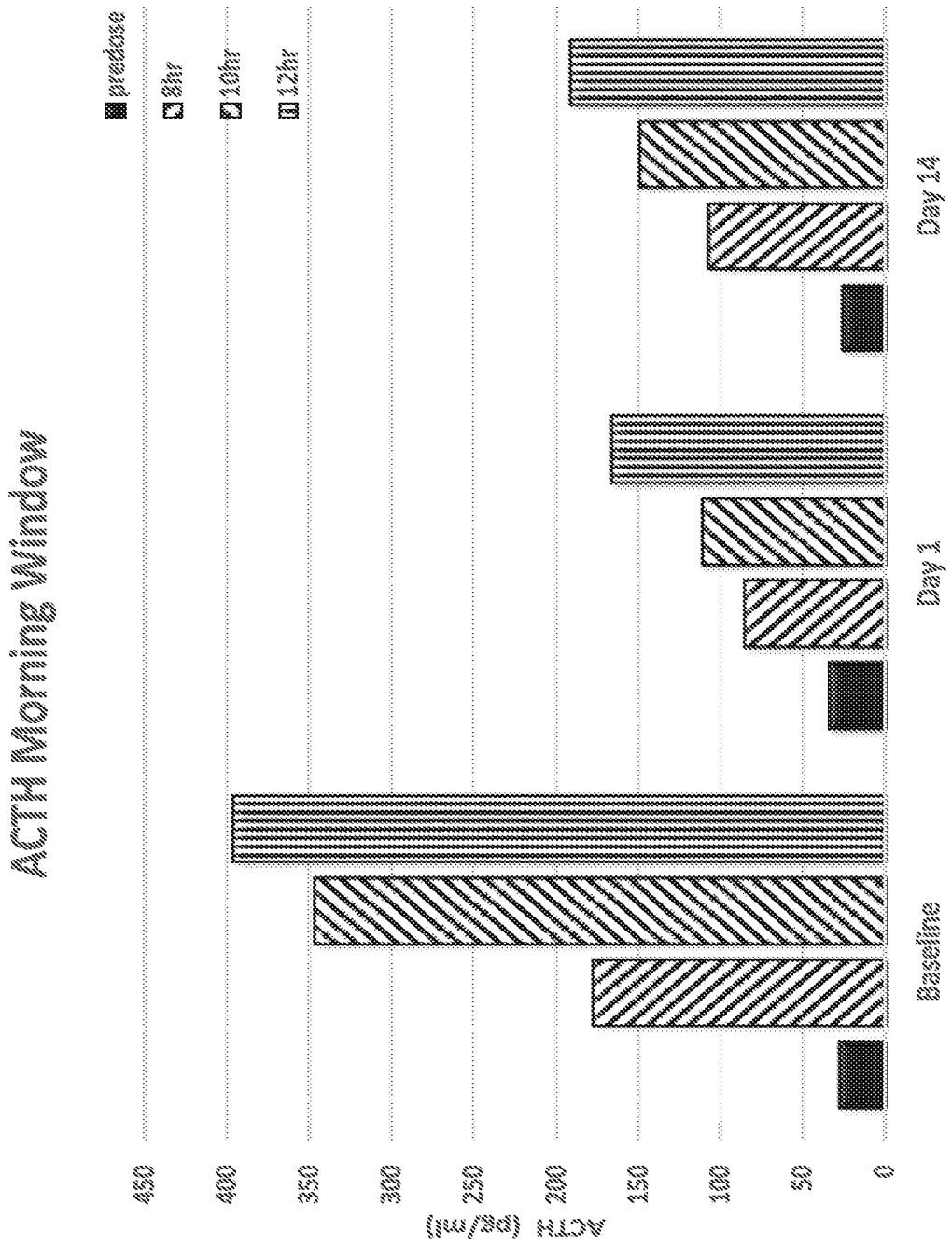

ACTH Morning Window
predose
8hr
10hr
12hr
ACTH (pg/ml)
450
400
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 14A

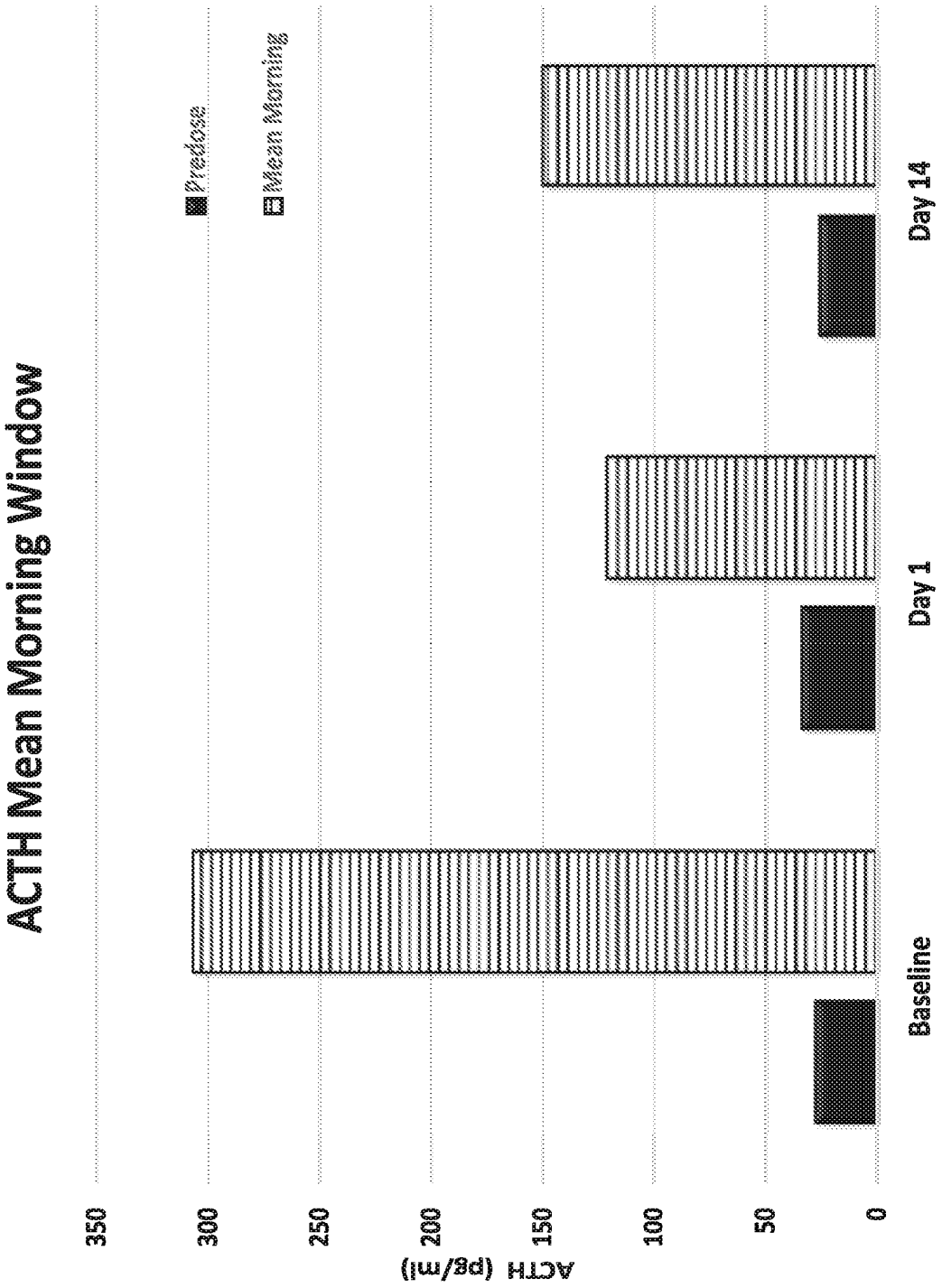

ACTH Mean Morning Window
Predose
Mean Morning
ACTH (pg/ml)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 14B

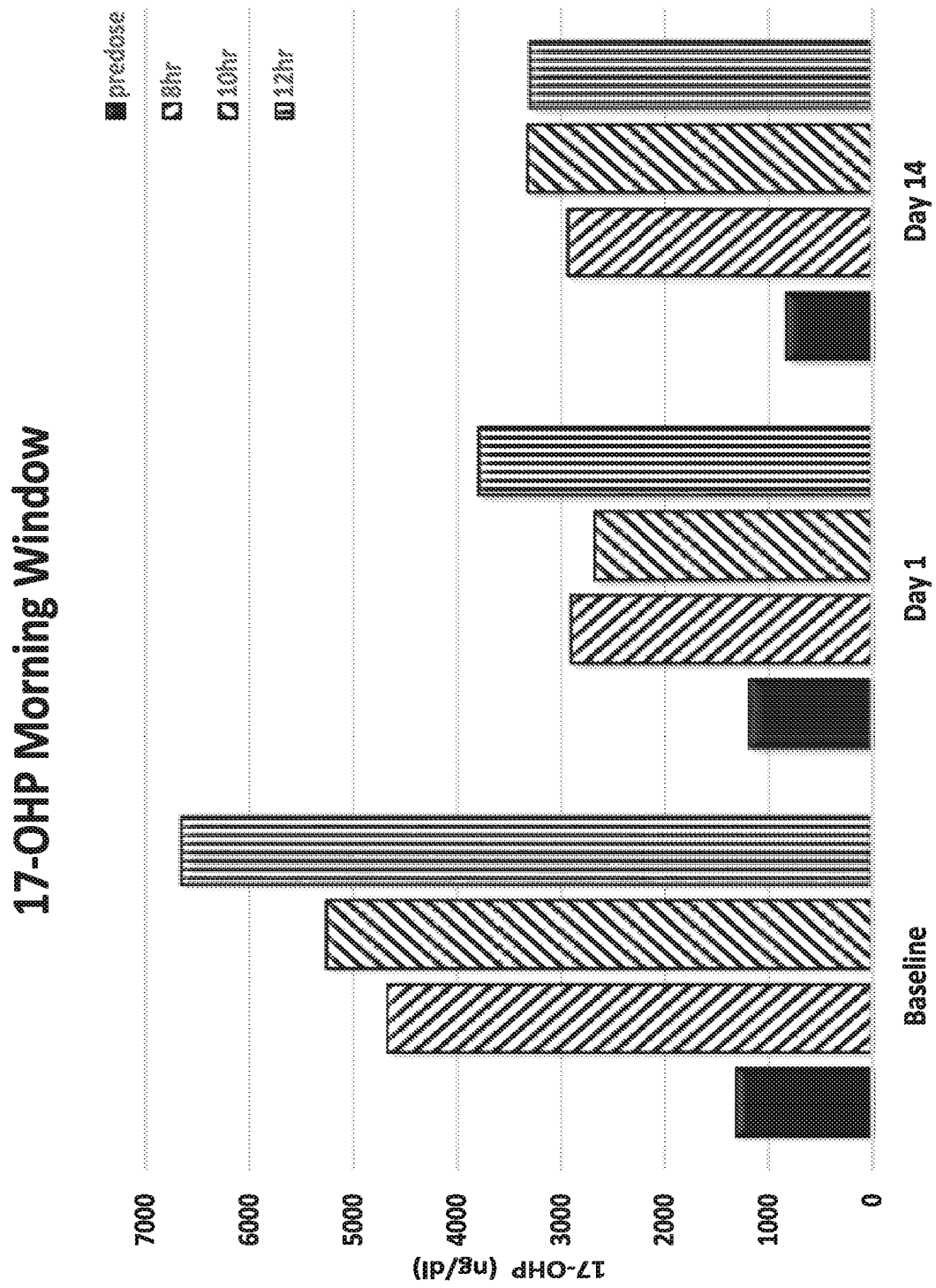

17-OHP Morning Window
predose
8hr
10hr
12hr
17-OHP (ng/dl)
7000
6000
5000
4000
3000
2000
1000
0
Baseline
Day 1
Day 14

FIG. 15A

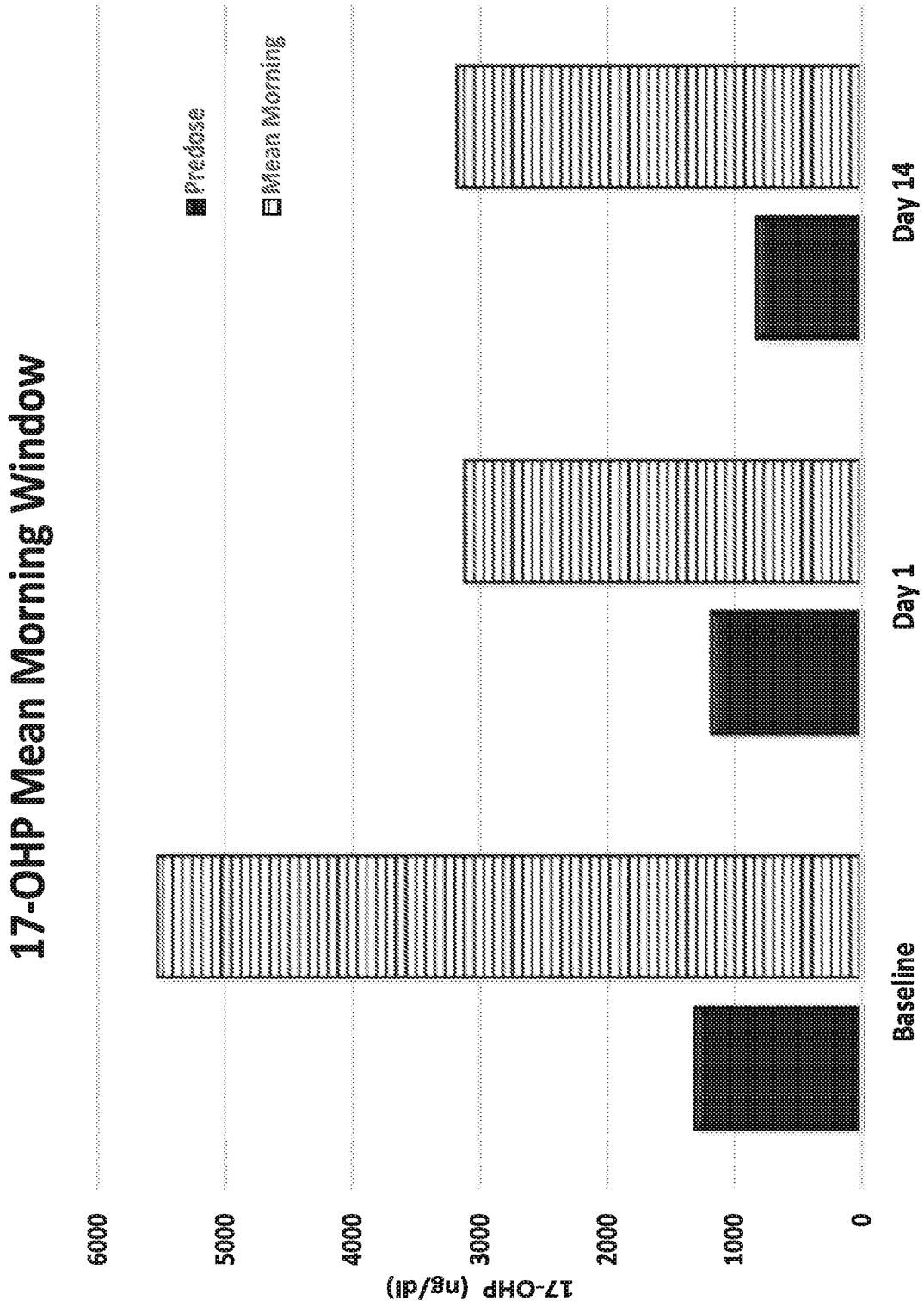

17-OHP Mean Morning Window
Predose
Mean Morning
17-OHP (ng/dl)
6000
5000
4000
3000
2000
1000
0
Baseline
Day 1
Day 14

FIG. 15B

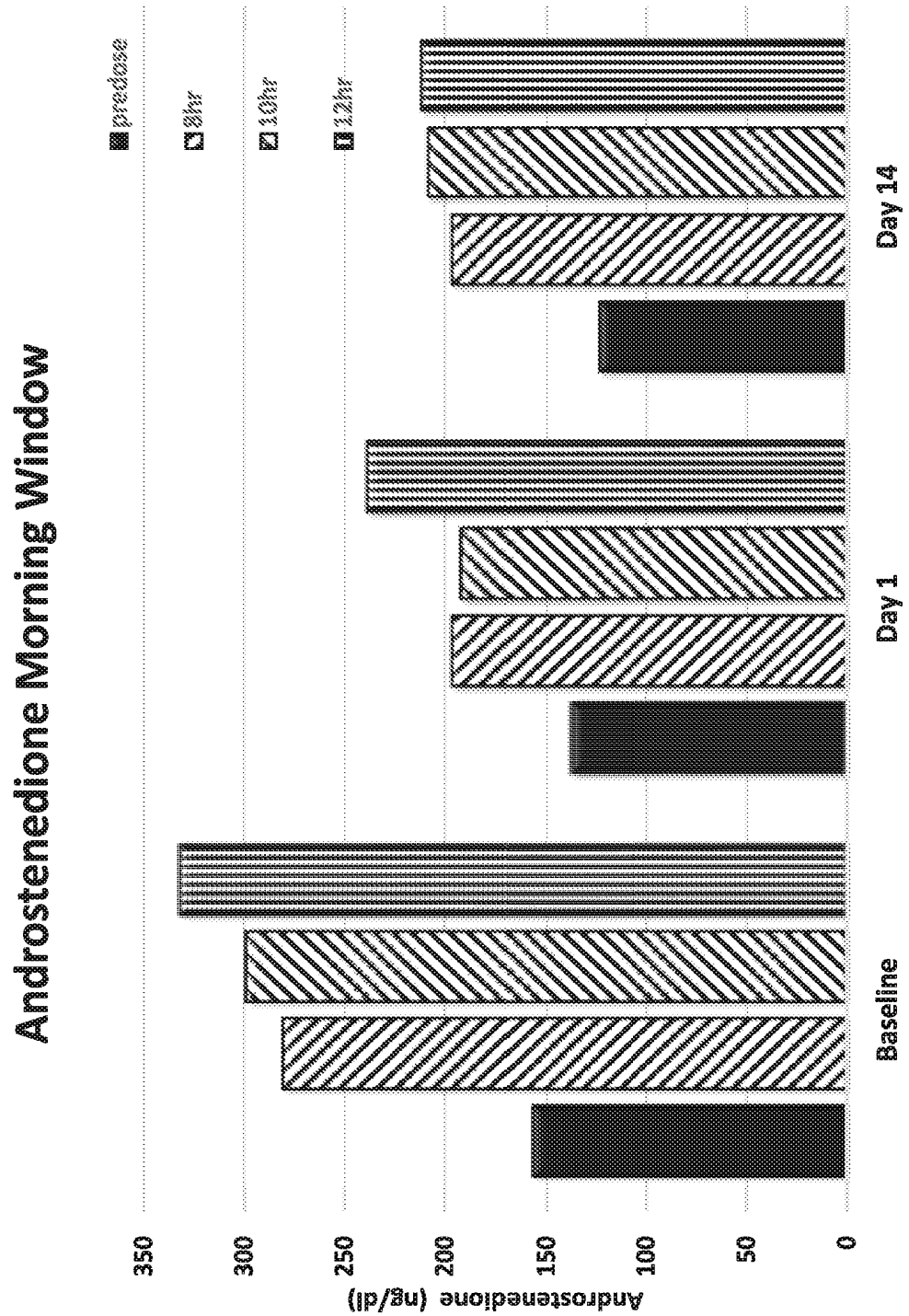

Androstenedione Morning Window
predose
8hr
10hr
12hr
Androstenedione (ng/dl)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 16A

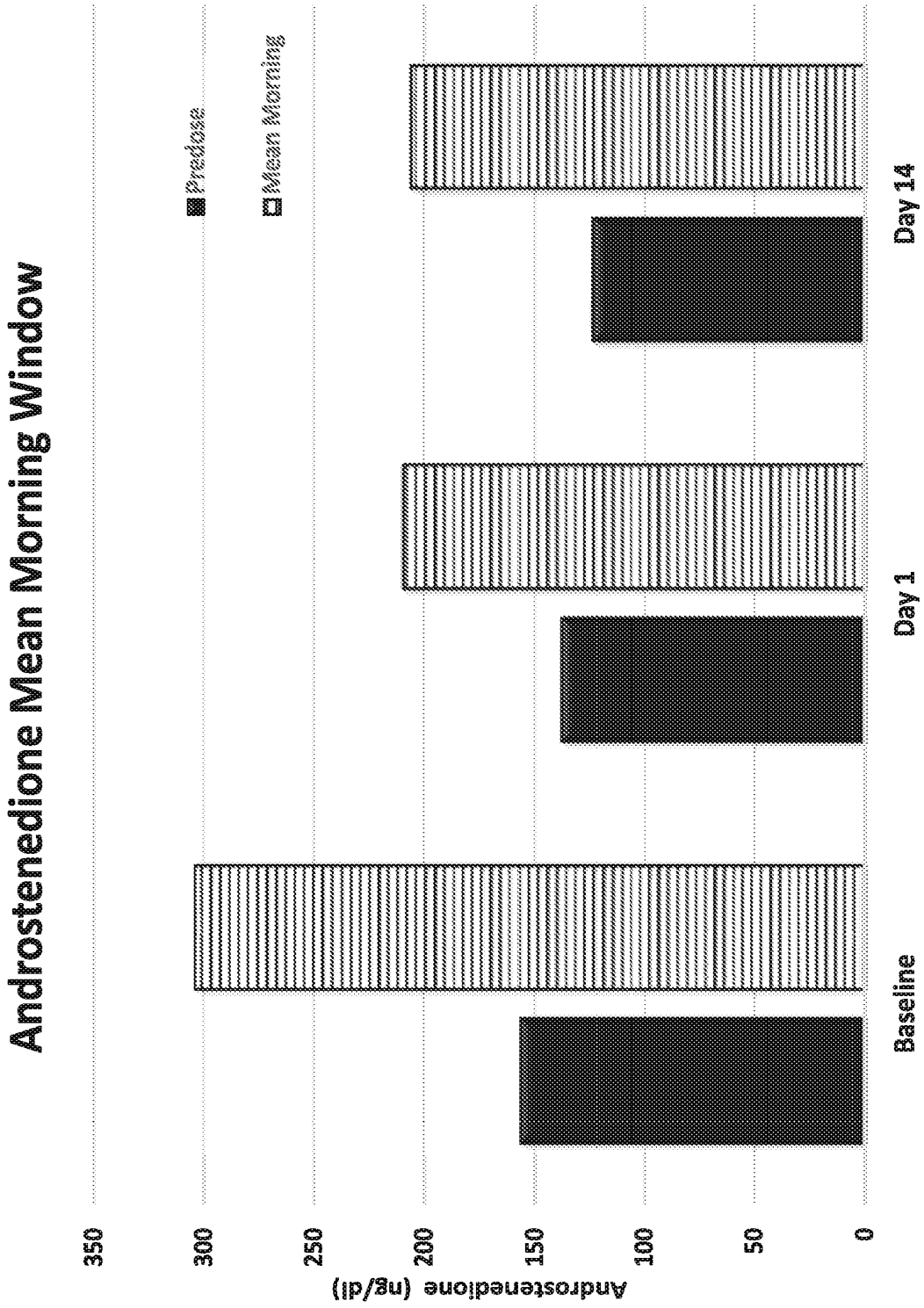

Androstenedione Mean Morning Window
Predose
Mean Morning
Androstenedione (ng/dl)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 16B

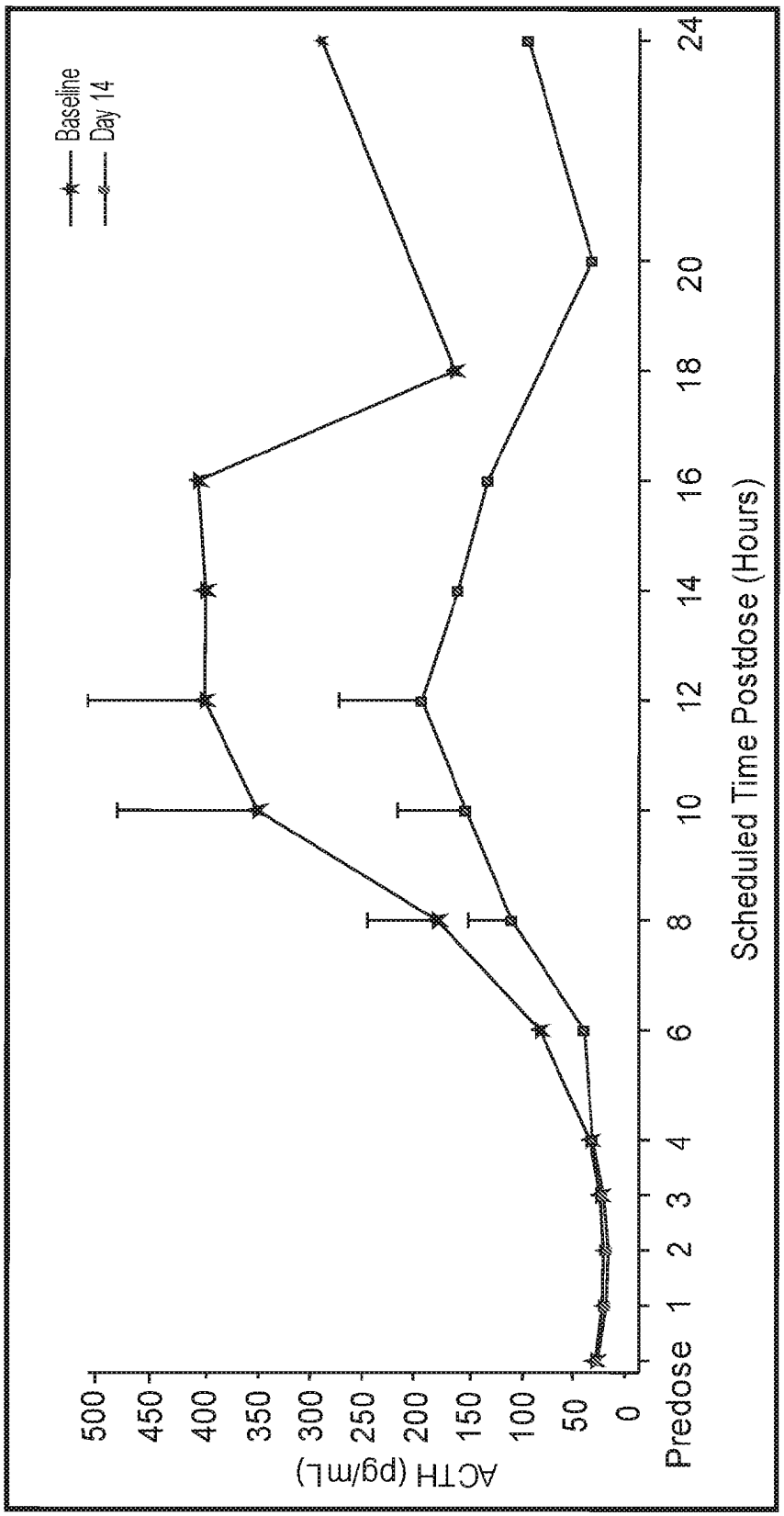

Baseline
Day 14
ACTH (pg/mL)
500
450
400
350
300
250
200
150
100
50
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 17A

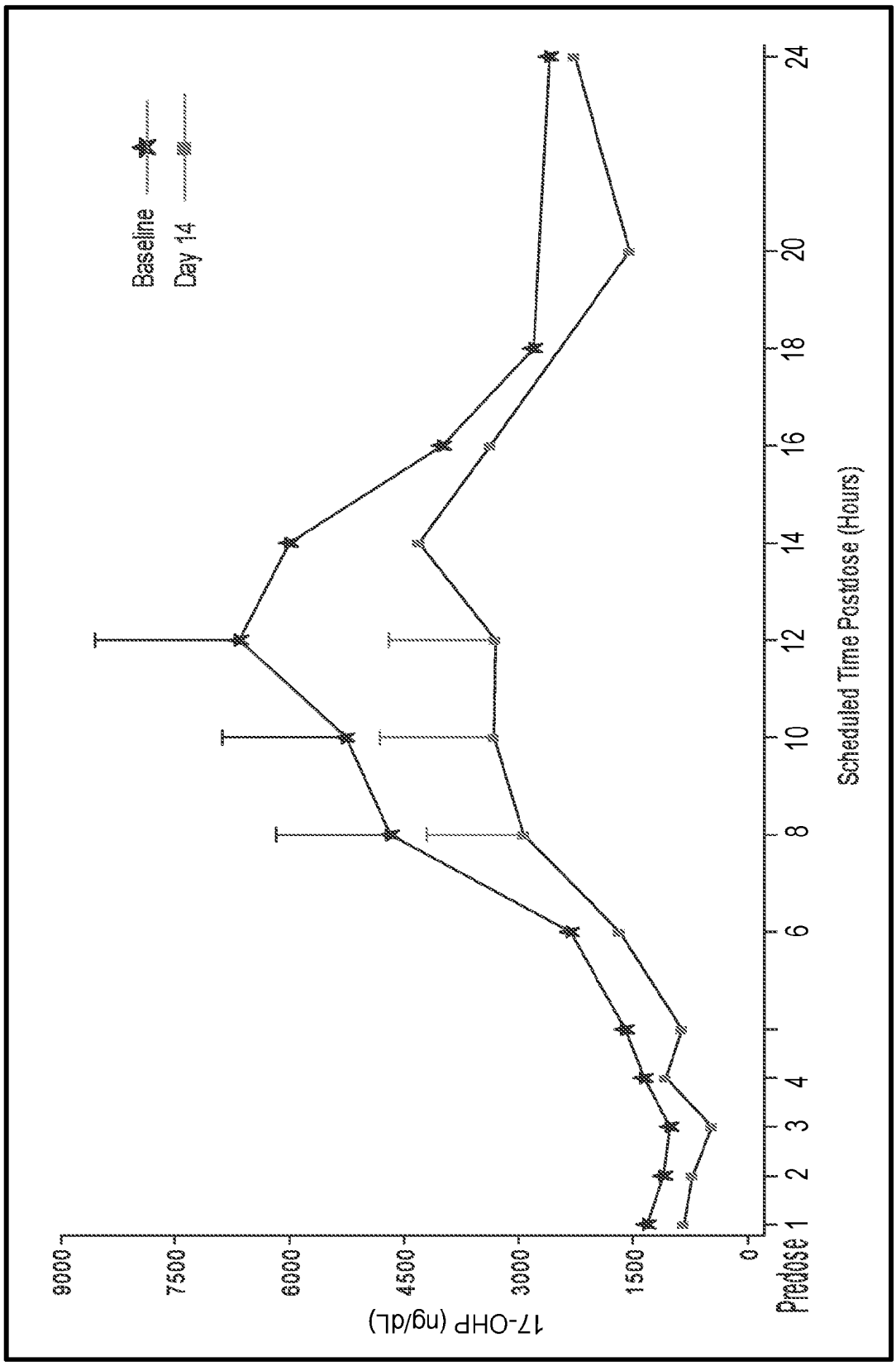

Baseline
Day 14
17-OHP (ng/dL)
9000
7500
6000
4500
3000
1500
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 17B

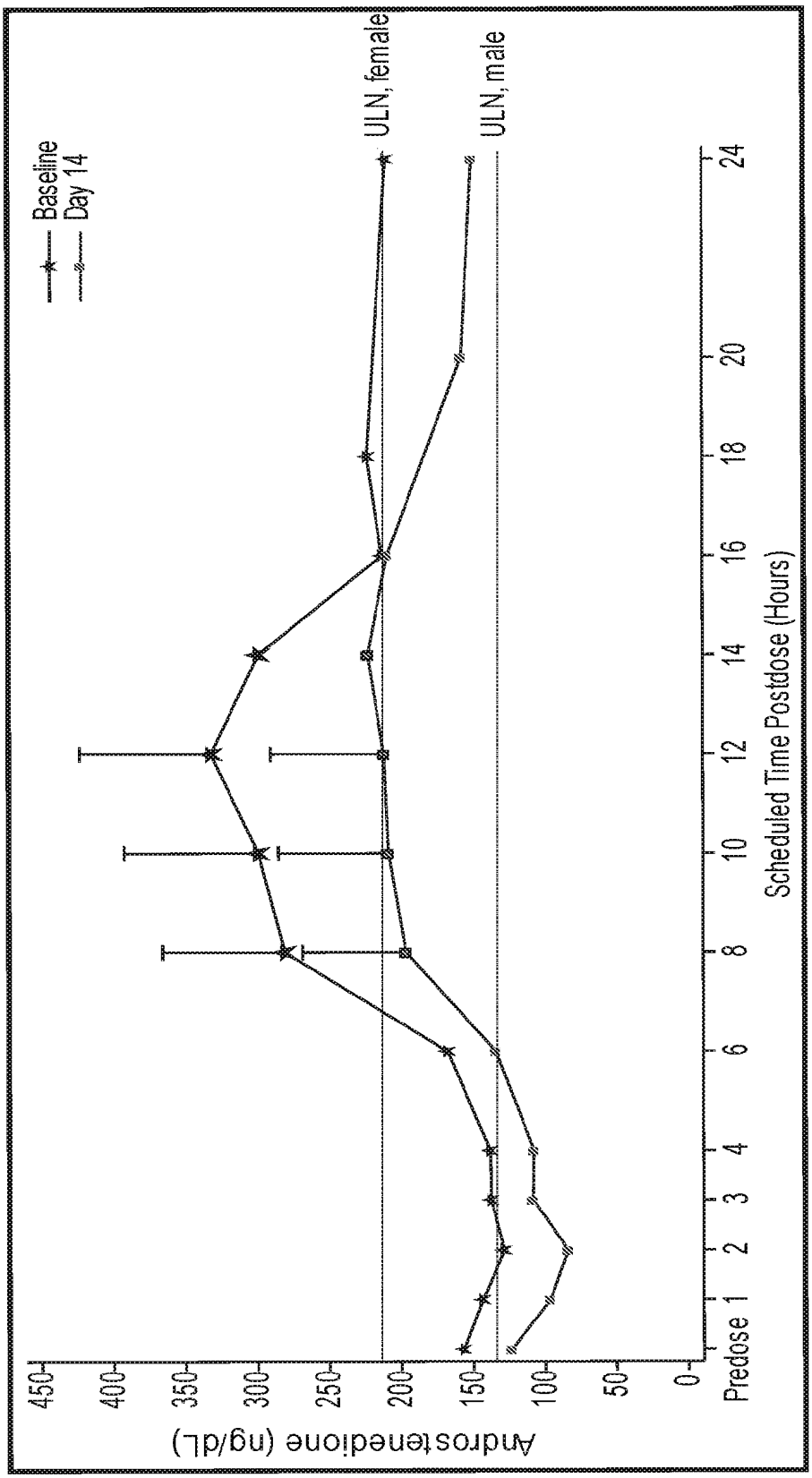

Androstenedione (ng/dL)
450
400
350
300
250
200
150
100
50
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)
ULN, female
ULN, male
Baseline
Day 14

FIG. 17C

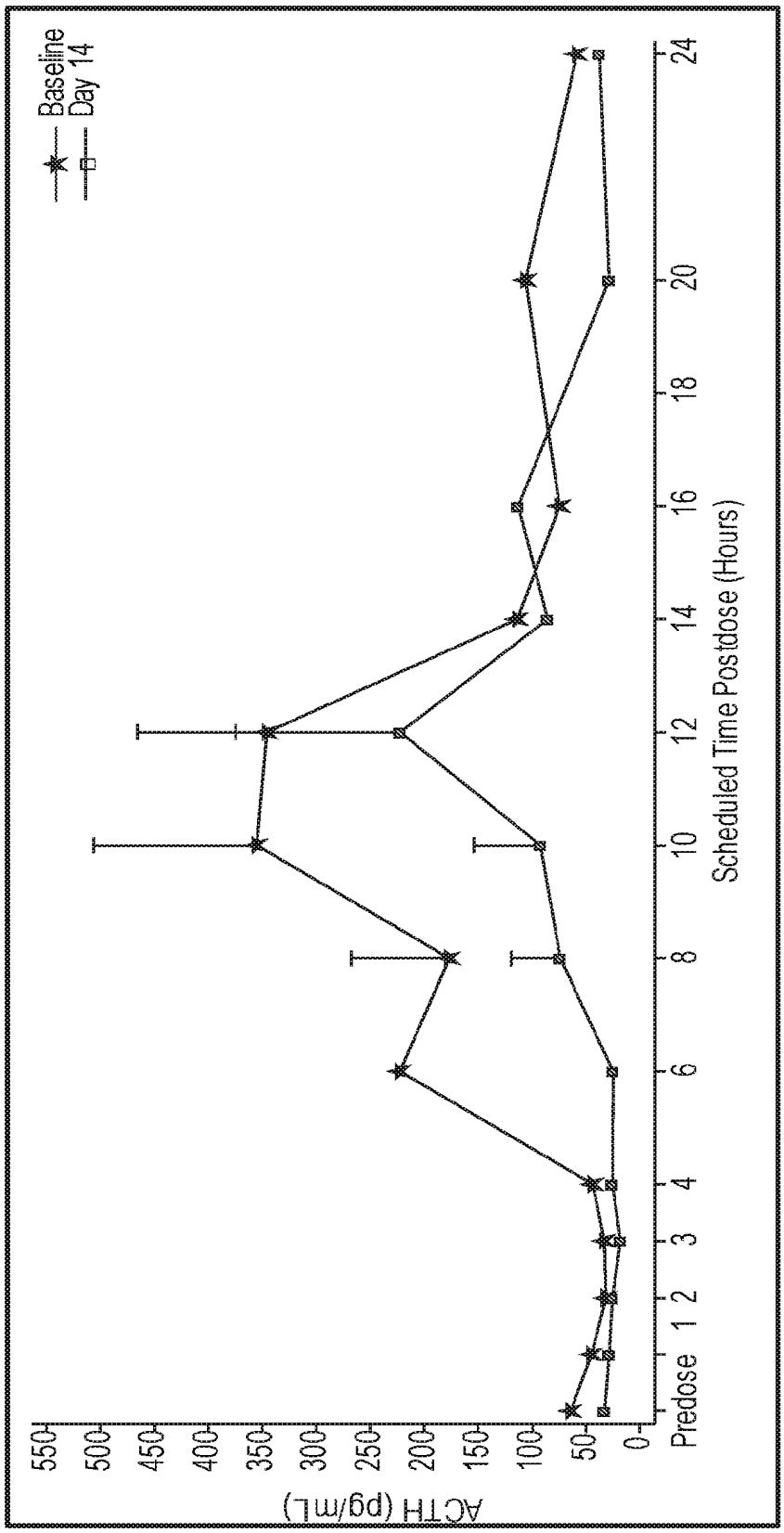

Baseline
Day 14
ACTH (pg/mL)
550
500
450
400
350
300
250
200
150
100
50
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 18A

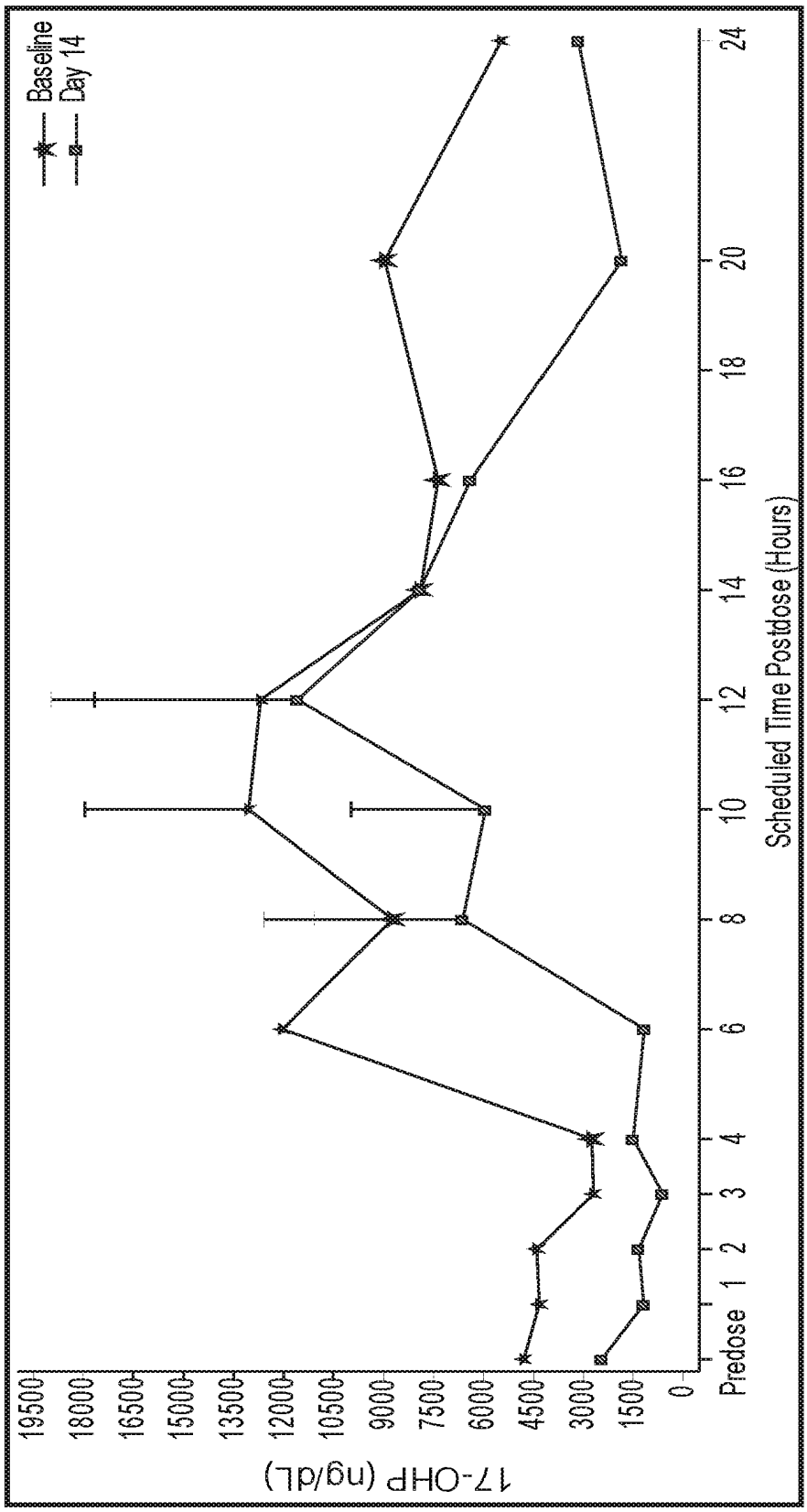

Baseline
Day 14
17-OHP (ng/dL)
19500
18000
16500
15000
13500
12000
10500
9000
7500
6000
4500
3000
1500
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 18B

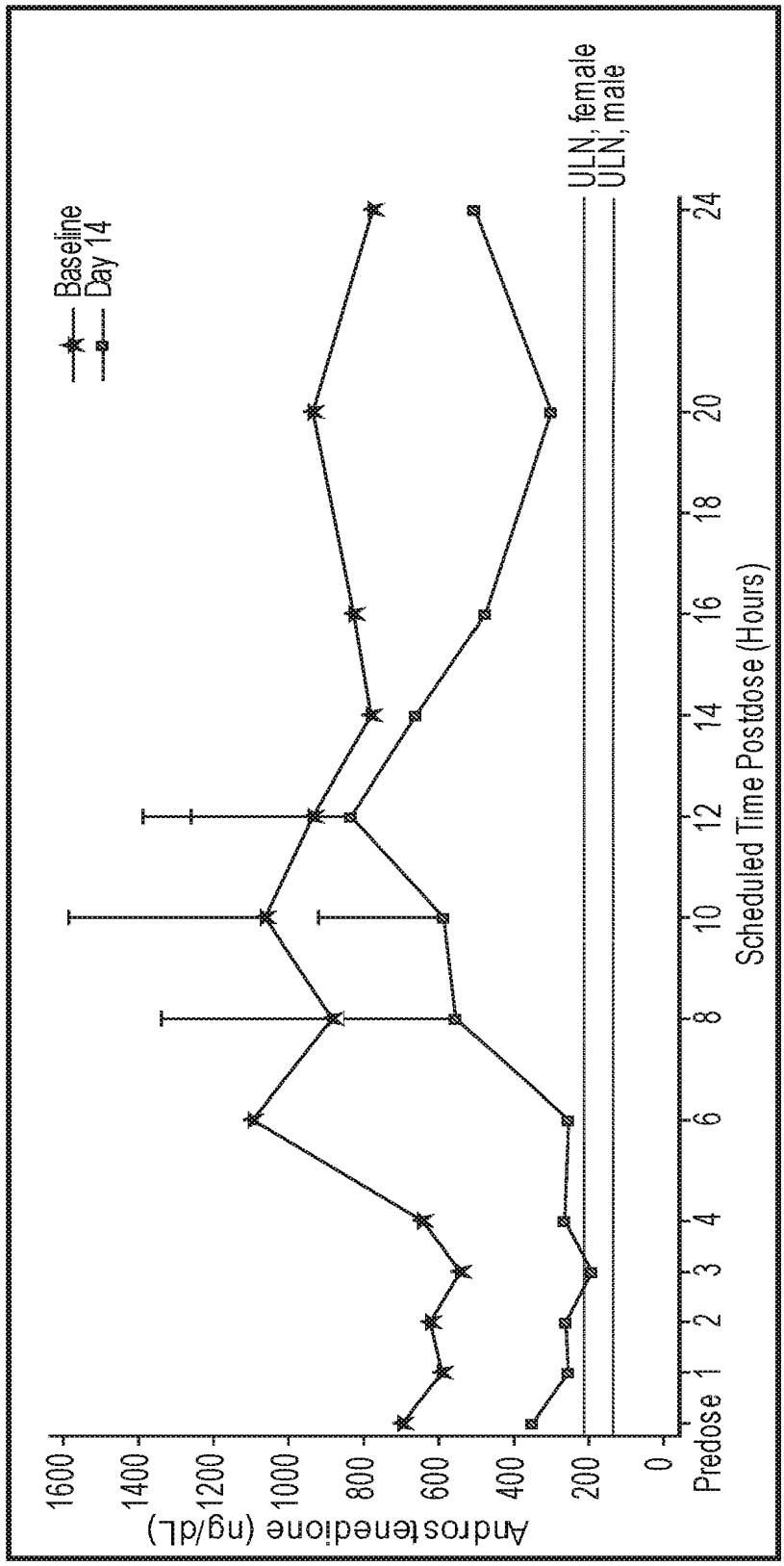

Baseline
Day 14
ULN, female
ULN, male
Androstenedione (ng/dL)
1600
1400
1200
1000
800
600
400
200
0
Predose 1 2 3 4 6 8 10 12 14 16 18 20 24
Scheduled Time Postdose (Hours)

FIG. 18C

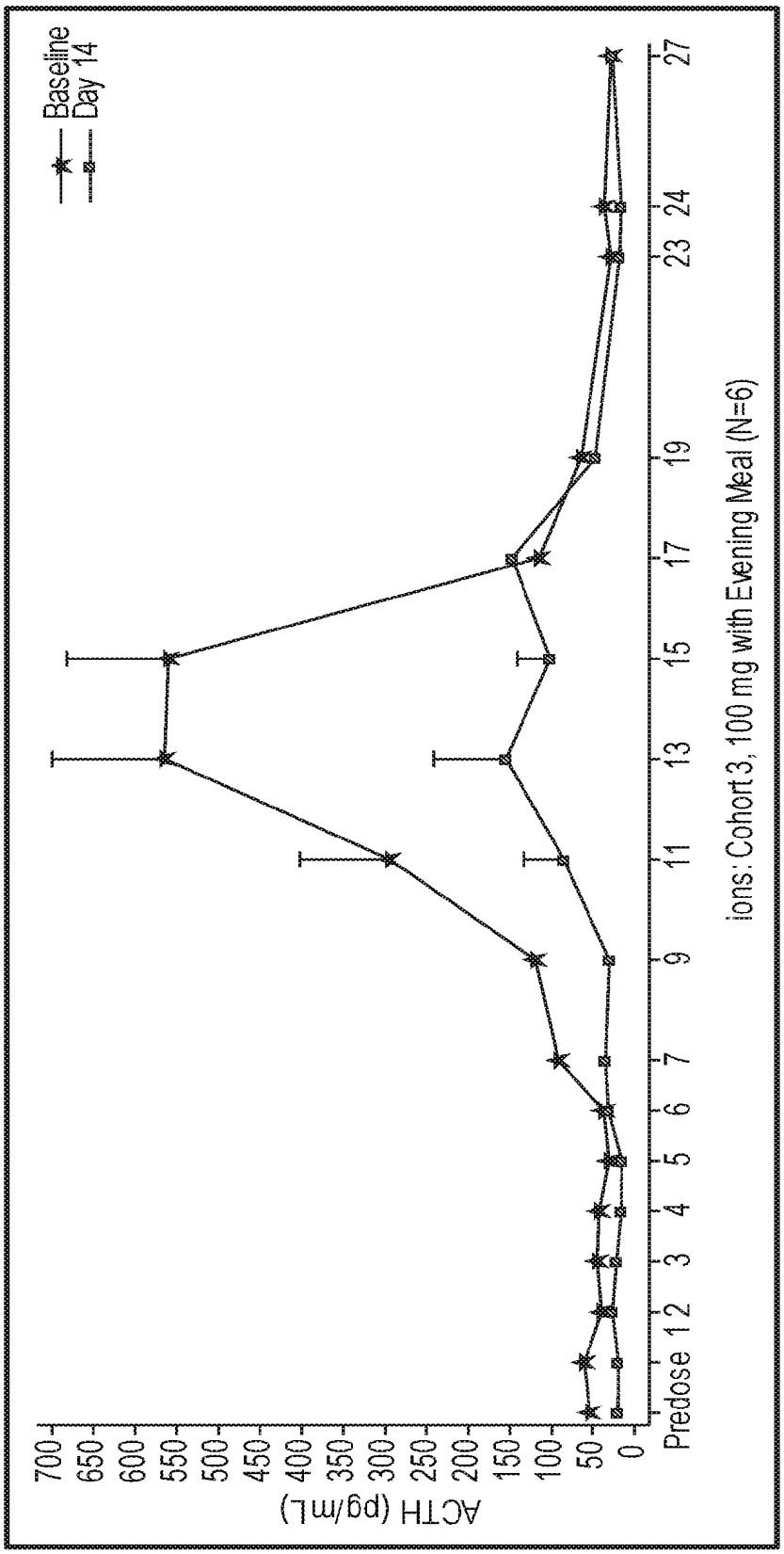

Baseline
Day 14
ACTH (pg/mL)
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
ions: Cohort 3, 100 mg with Evening Meal (N=6)

FIG. 19A

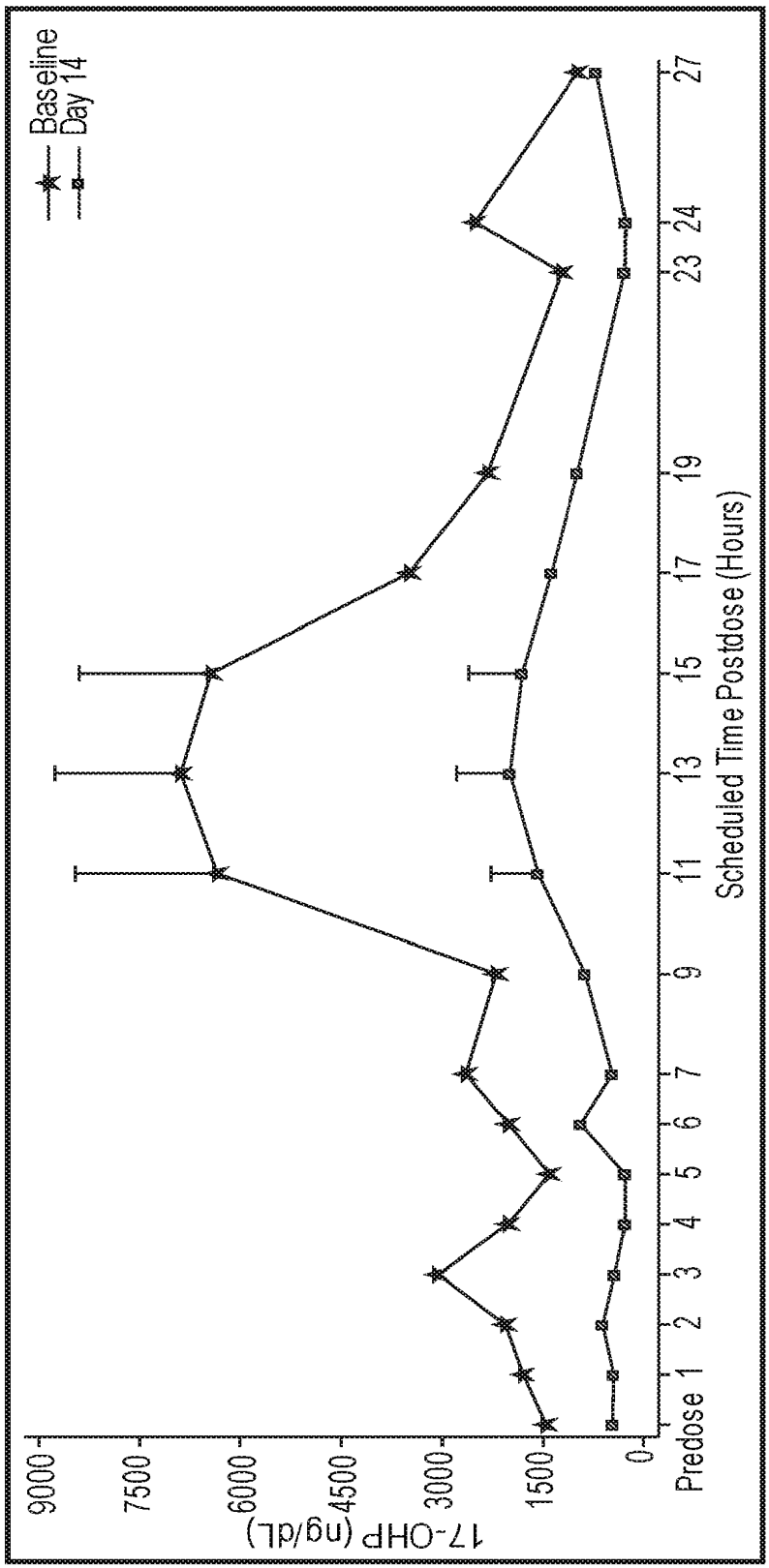

Baseline
Day 14
17-OHP (ng/dL)
9000
7500
6000
4500
3000
1500
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
Scheduled Time Postdose (Hours)

FIG. 19B

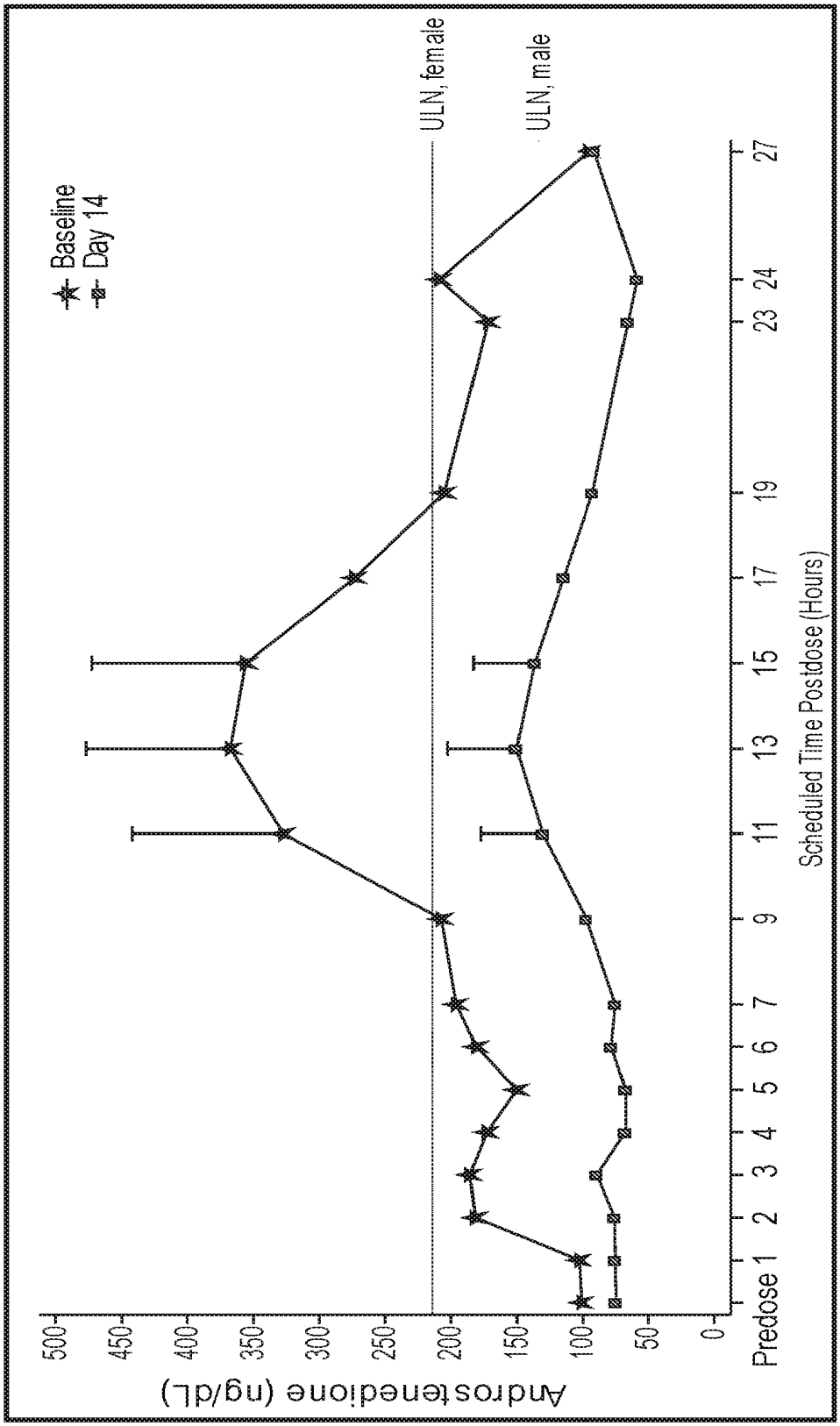

Baseline
Day 14
ULN, female
ULN, male
Androstenedione (ng/dL)
500
450
400
350
300
250
200
150
100
50
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
Scheduled Time Postdose (Hours)

FIG. 19C

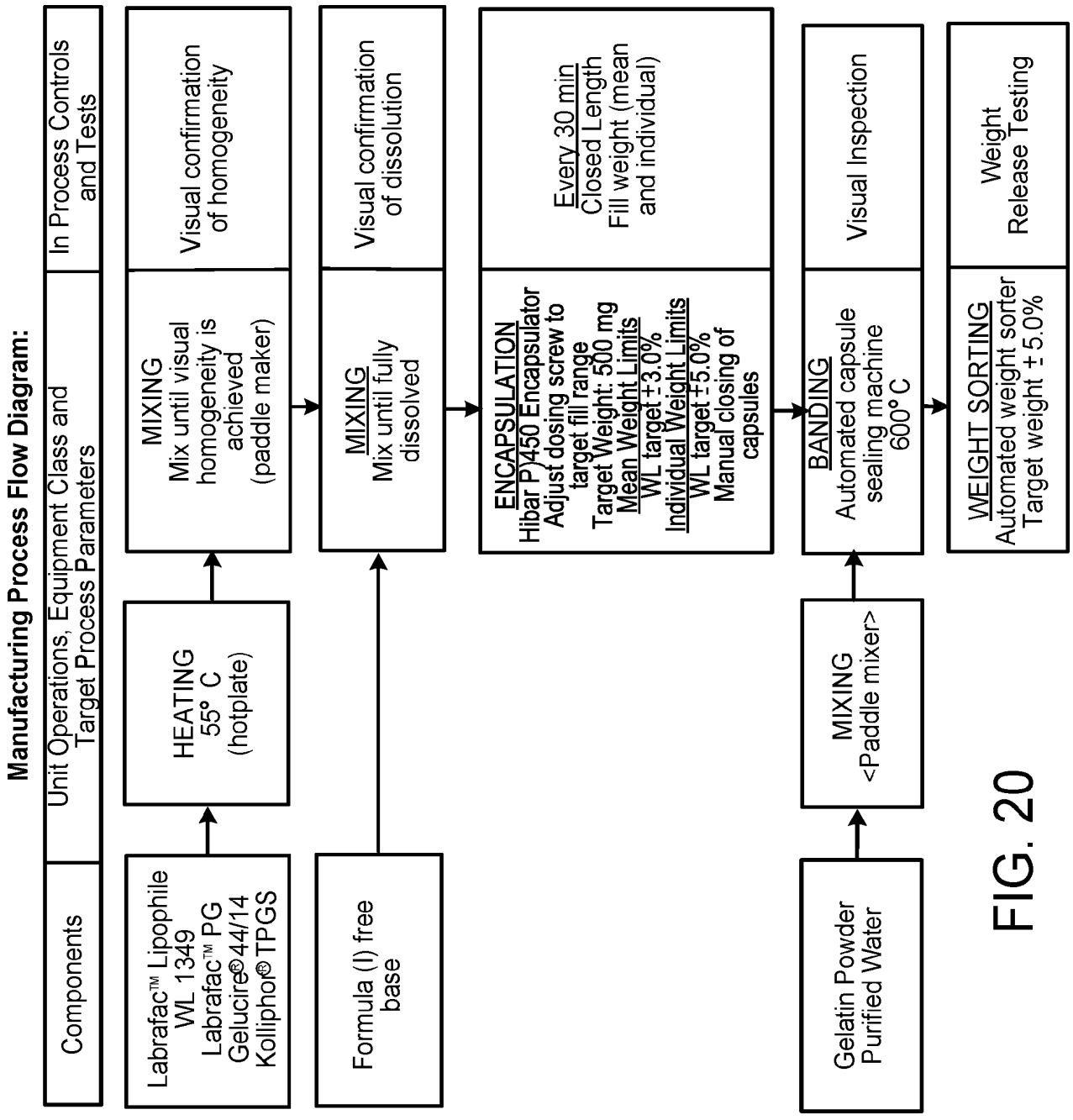
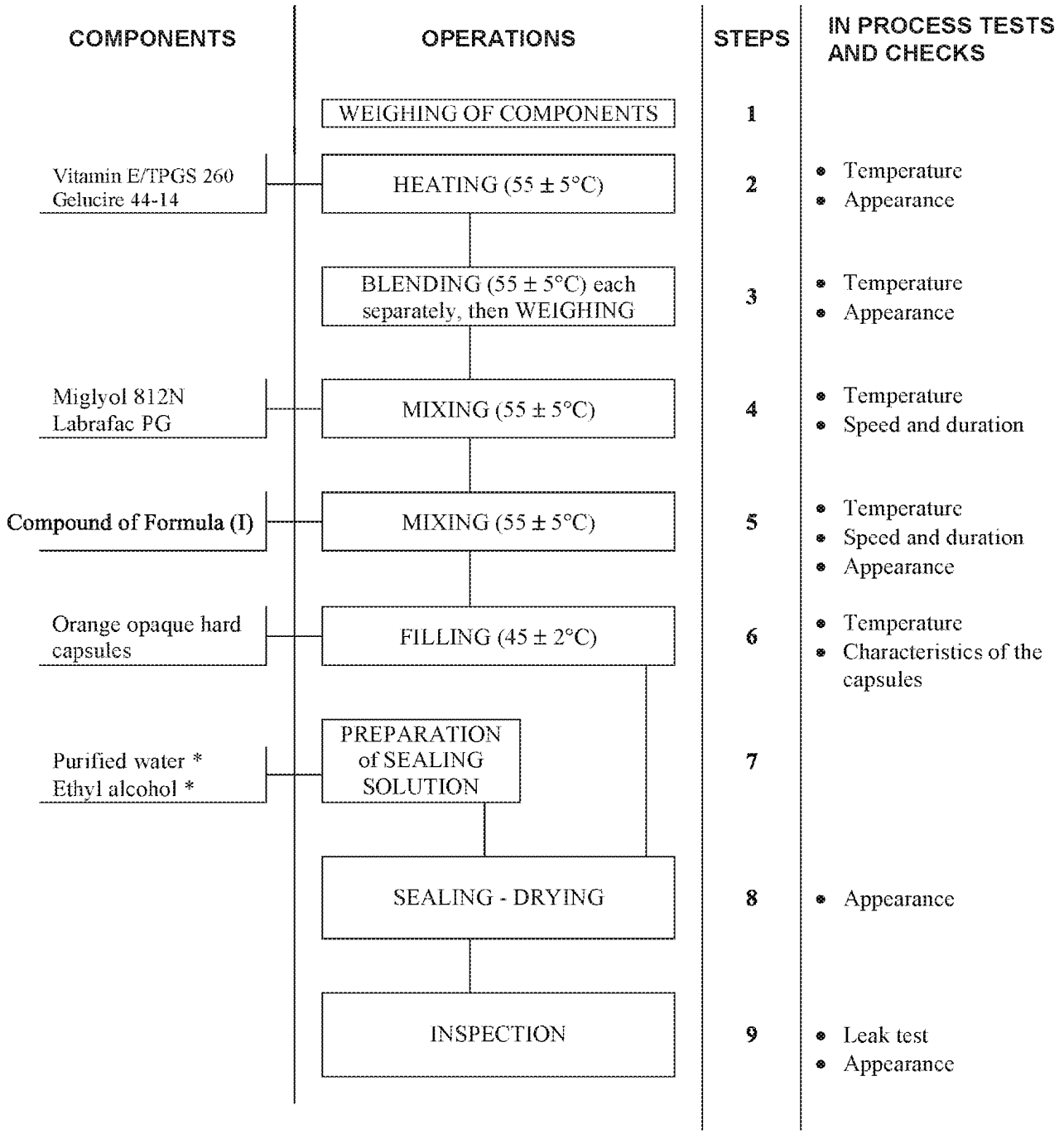

Manufacturing Process Flow Diagram:
Components
Unit Operations, Equipment Class and Target Process Parameters
In Process Controls and Tests
Labrafac™ Lipophile WL 1349
Labrafac™ PG
Gelucire® 44/14
Kolliphor® TPGS
HEATING
55° C
(hotplate)
MIXING
Mix until visual homogeneity is achieved
(paddle maker)
Visual confirmation of homogeneity
Formula (I) free base
MIXING
Mix until fully dissolved
Visual confirmation of dissolution
ENCAPSULATION
Hibar P/450 Encapsulator
Adjust dosing screw to target fill range
Target Weight: 500 mg
Mean Weight Limits
WL target ±3.0%
Individual Weight Limits
WL target ±5.0%
Manual closing of capsules
Every 30 min
Closed Length
Fill weight (mean and individual)
Gelatin Powder
Purified Water
MIXING
<Paddle mixer>
BANDING
Automated capsule sealing machine
600° C
Visual Inspection
WEIGHT SORTING
Automated weight sorter
Target weight ± 5.0%
Weight
Release Testing

FIG. 20




* Can be contained in hydro-alcoholic solution ready for manufacturing use

FIG. 21

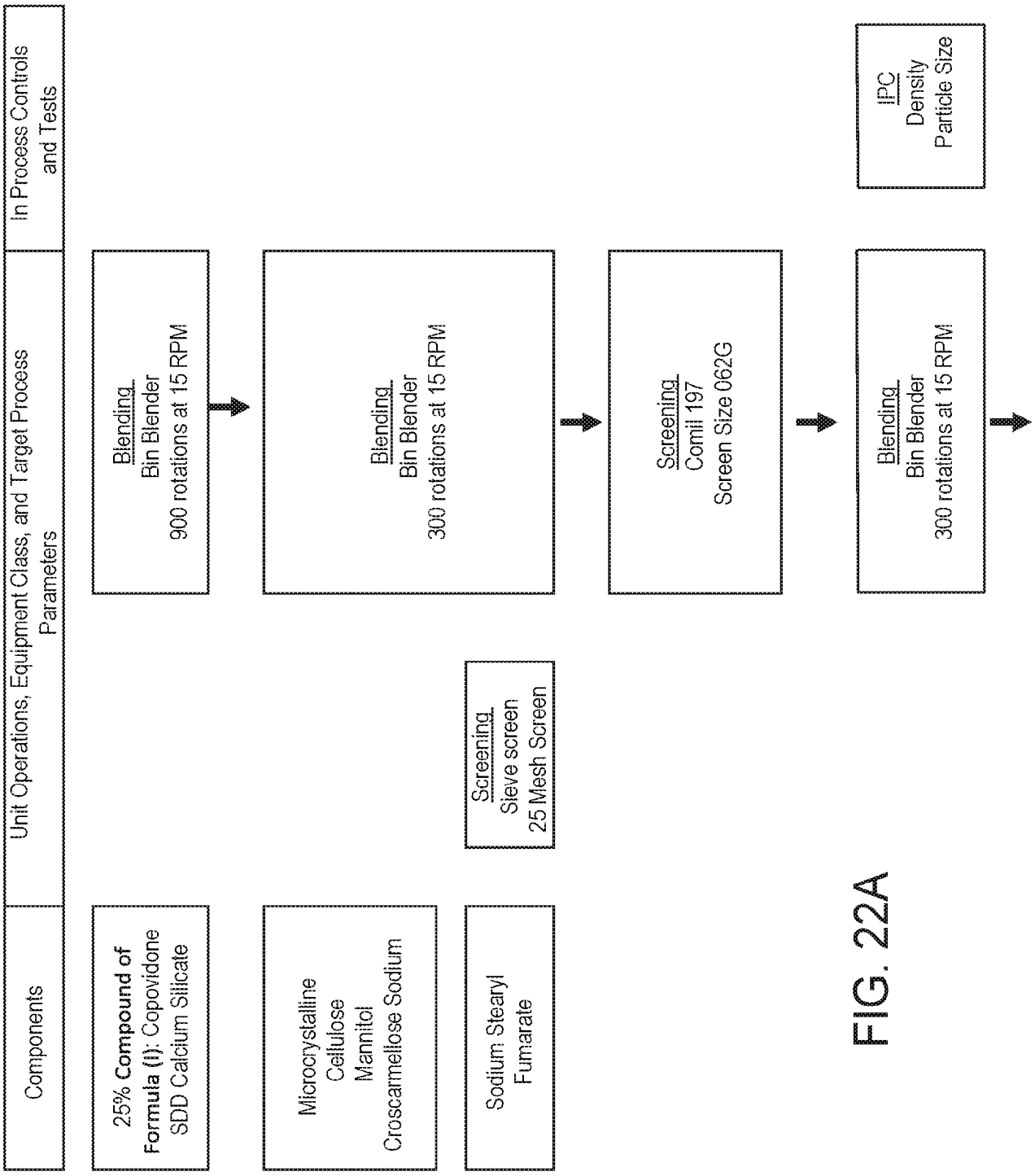

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
25% Compound of Formula (I): Copovidone SDD Calcium Silicate
Microcrystalline Cellulose Mannitol Croscarmellose Sodium
Sodium Stearyl Fumarate
Blending
Bin Blender
900 rotations at 15 RPM
Screening
Sieve screen
25 Mesh Screen
Blending
Bin Blender
300 rotations at 15 RPM
Screening
Comil 197
Screen Size 062G
Blending
Bin Blender
300 rotations at 15 RPM
IPC
Density
Particle Size

FIG. 22A

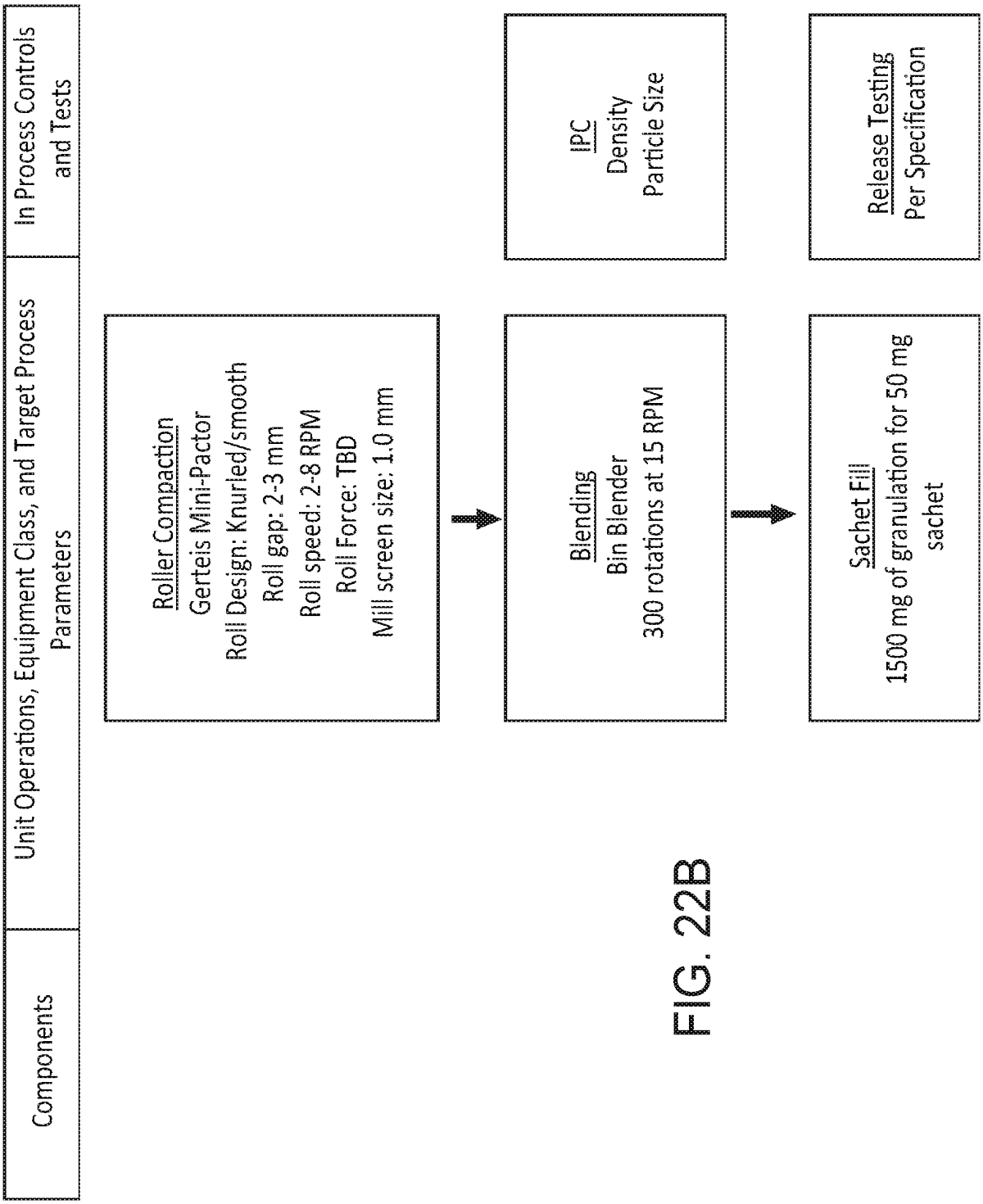

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
Roller Compaction
Gerteis Mini-Pactor
Roll Design: Knurled/smooth
Roll gap: 2-3 mm
Roll speed: 2-8 RPM
Roll Force: TBD
Mill screen size: 1.0 mm
Blending
Bin Blender
300 rotations at 15 RPM
IPC
Density
Particle Size
Sachet Fill
1500 mg of granulation for 50 mg sachet
Release Testing
Per Specification

FIG. 22B

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
75% of Total Medium Chain Triglycerides Saccharin
Mix with overhead Mixer to create a medium vortex
(This step may require temperature control, studies on-going)
Butylated Hydroxytoluene Orange Flavor
Mix with overhead Mixer to create a medium vortex
Compound of Formula (I)
Mix with overhead Mixer to create a medium vortex
Remaining 25% of Medium Chain Triglycerides
Mix with overhead Mixer to create a medium vortex
Bottle Filling
IPC
Label Claim Check
IPC
Fill Weight Checks
Release Testing
See Specification

FIG. 23

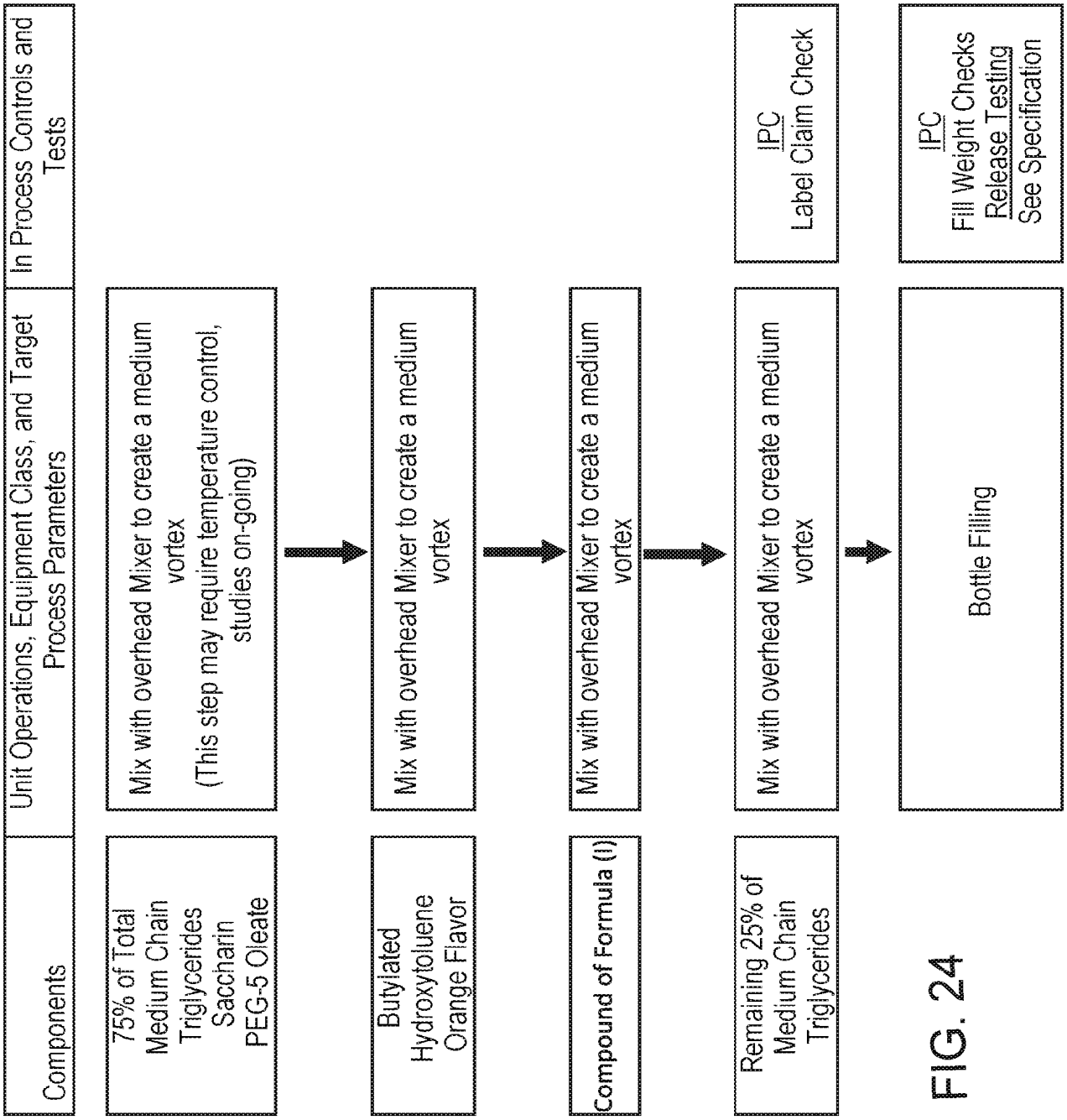

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
75% of Total Medium Chain Triglycerides
Saccharin
PEG-5 Oleate
Mix with overhead Mixer to create a medium vortex
(This step may require temperature control, studies on-going)
Butylated Hydroxytoluene
Orange Flavor
Mix with overhead Mixer to create a medium vortex
Compound of Formula (I)
Mix with overhead Mixer to create a medium vortex
Remaining 25% of Medium Chain Triglycerides
Mix with overhead Mixer to create a medium vortex
IPC
Label Claim Check
Bottle Filling
IPC
Fill Weight Checks
Release Testing
See Specification

FIG. 24

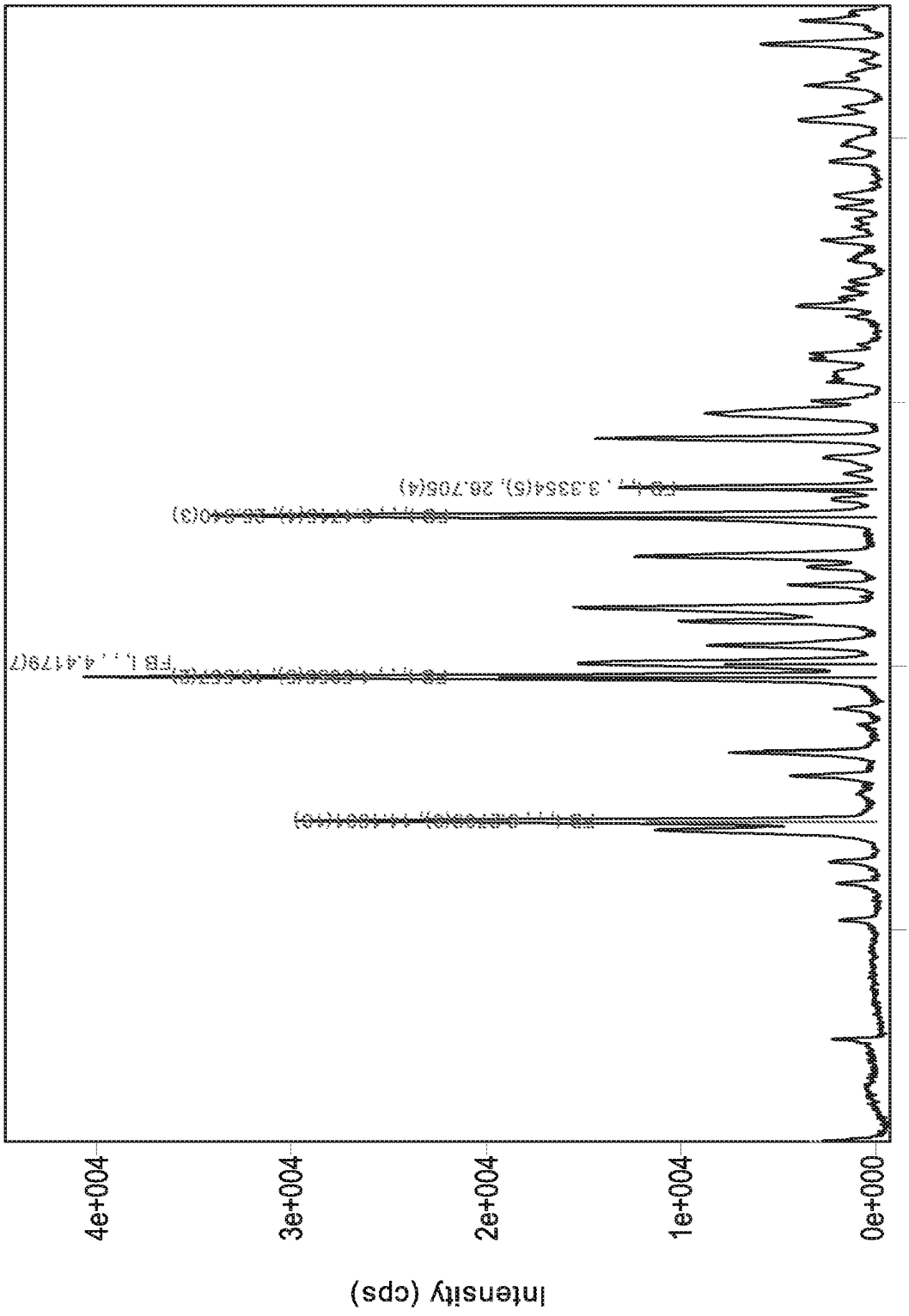

Intensity (cps)
0e+000
1e+004
2e+004
3e+004
4e+004
10
20
30
40
2-theta (deg)

FIG. 25

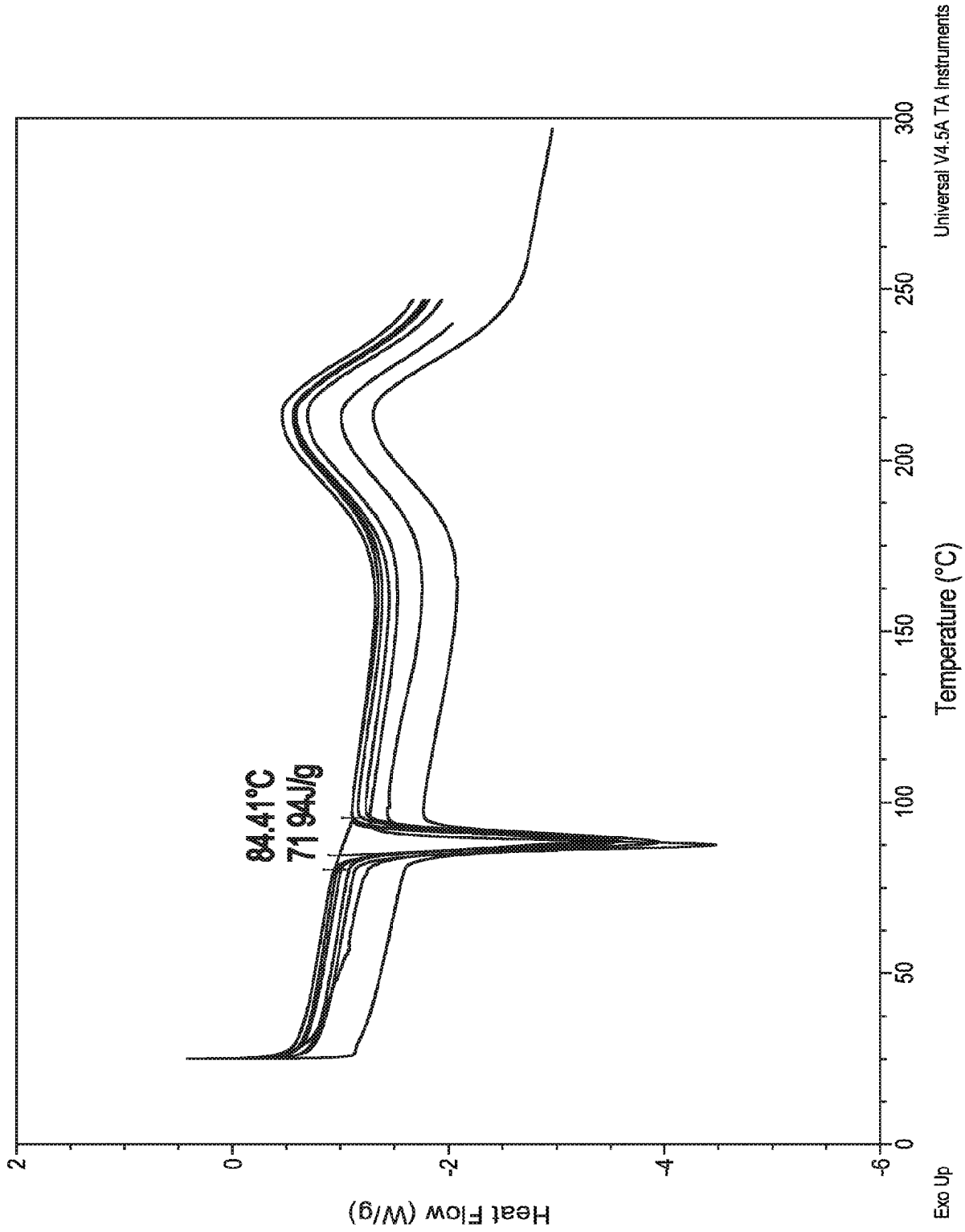

84.41°C
71.94J/g
Heat Flow (W/g)
Exo Up
Temperature (°C)
Universal V4.5A TA Instruments
2
0
-2
-4
-6
0
50
100
150
200
250
300

FIG. 26

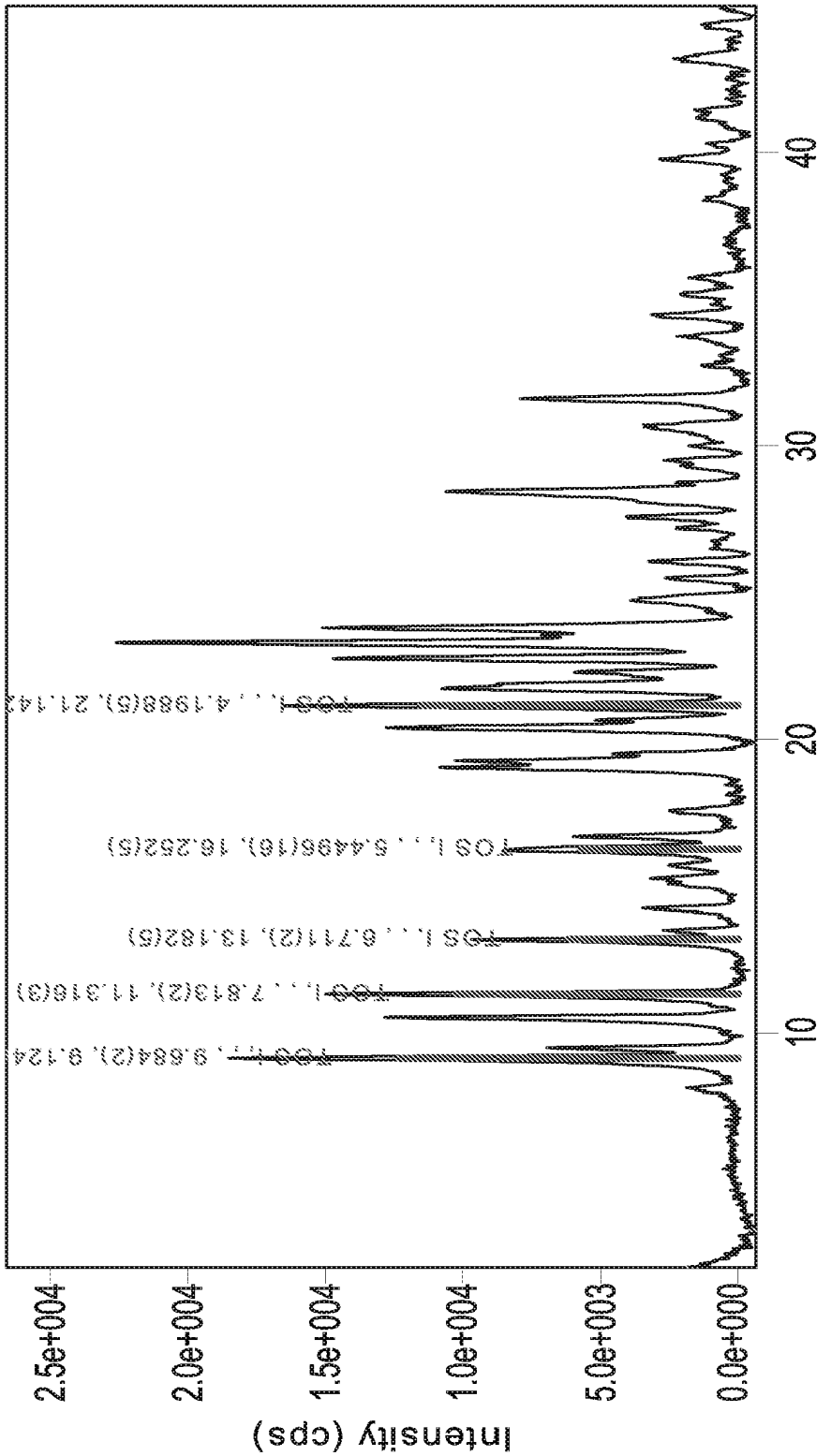

Intensity (cps)
2.5e+004
2.0e+004
1.5e+004
1.0e+004
5.0e+003
0.0e+000
2-theta (deg)
10
20
30
40

FIG. 27

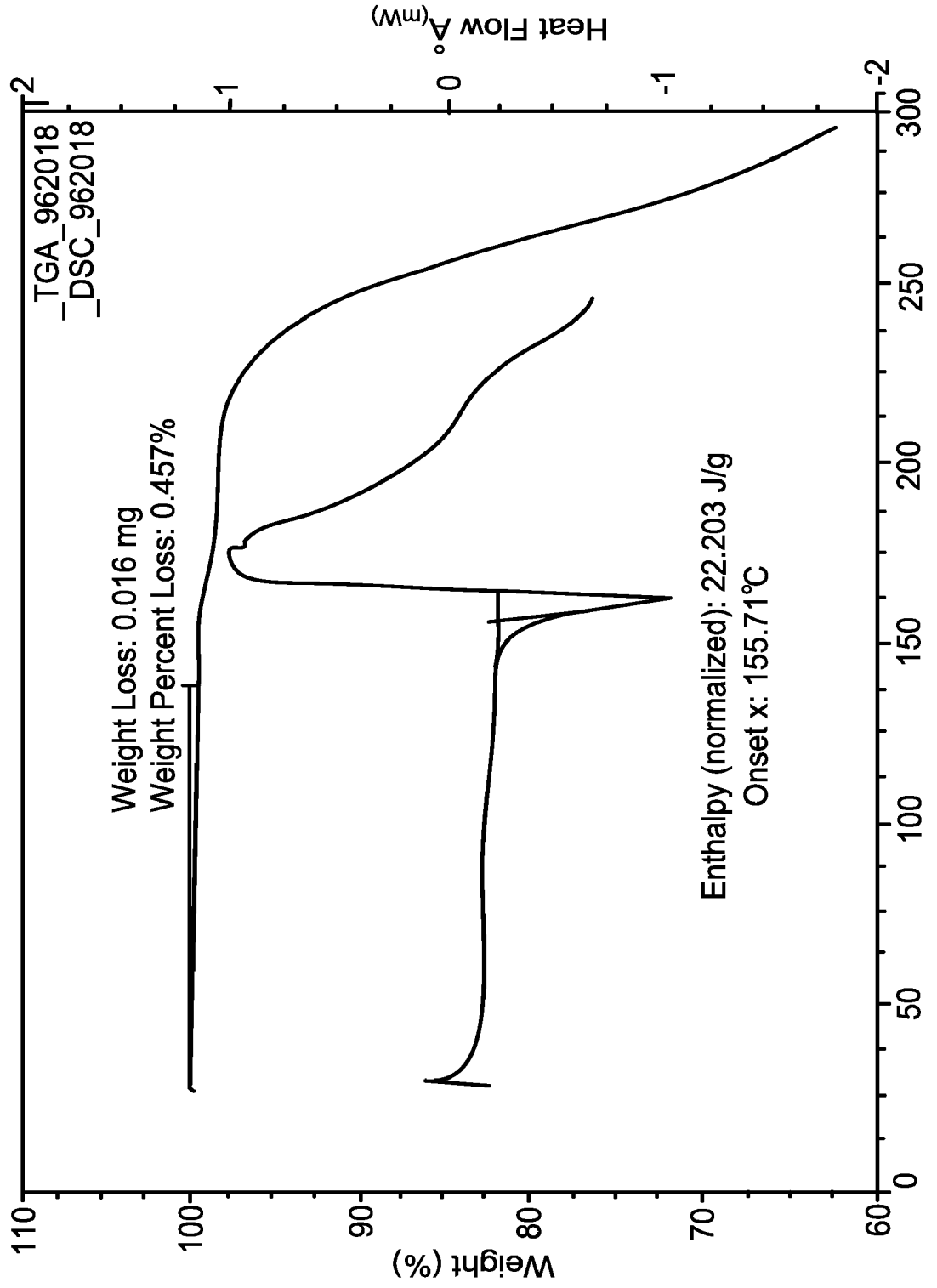

_TGA_962018
_DSC_962018
Weight Loss: 0.016 mg
Weight Percent Loss: 0.457%
Enthalpy (normalized): 22.203 J/g
Onset x: 155.71°C
Weight (%)
Heat Flow A° (mW)
Temperature (°C)
110
100
90
80
70
60
2
1
0
-1
-2
0
50
100
150
200
250
300

FIG. 28

Europäisches Patentamt
European Patent Office
Office européen des brevets

# EUROPEAN SEARCH REPORT

Application Number
EP 21 21 3854

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (IPC) |
|---|---|---|---|
| X | WO 2015/112642 A1 (NEUROCRINE BIOSCIENCES INC [US]) 30 July 2015 (2015-07-30)<br>* SSR-125543;<br>page 14 *<br>* claims 1-21 * | 1-166 | INV.<br>A61K9/00<br>A61K31/395<br>A61K31/426<br>A61K31/573<br>A61P5/00 |
| A | WO 2010/125414 A1 (SANOFI-AVENTIS [FR]; PARKANYI ZSOLT [HU] ET AL.)<br>4 November 2010 (2010-11-04)<br>* the whole document * | 1-166 | |
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TECHNICAL FIELDS SEARCHED (IPC)

A61K

1 The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| Munich | 14 March 2022 | Schüle, Stefanie |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

# ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 21 21 3854

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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14-03-2022

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(54) **Title:** METHODS AND COMPOSITIONS FOR TREATING POLYCYSTIC OVARY SYNDROME

(57) **Abstract:** Polycystic ovary syndrome (PCOS) is characterized by elevated levels of androgens, cysts in the ovaries, and irregular periods. Women with PCOS present with additional symptoms, including hirsutism, alopecia, acne, infertility, weight gain, fatigue, depression and mood changes. The present disclosure provides new compounds, salts, compositions and uses thereof in the treatment of PCOS due to elevated adrenal androgens. Further, the present disclosure provides methods for treating PCOS due to elevated adrenal androgens.

WO 2022/036123 A1

# METHODS AND COMPOSITIONS FOR TREATING POLYCYSTIC OVARY SYNDROME

## CROSS-REFERENCE

**[0001]** This application claims the benefit of U.S. Provisional Patent Application No. 63/064,863, filed August 12, 2020; which is referenced herein in its entirety.

## BACKGROUND

**[0002]** Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting an estimated 12% of reproductive aged women. Women with PCOS may have polycystic ovarian morphologic features, ovulatory dysfunction in the form of infrequent or prolonged menstrual periods, and hyperandrogenism in the form of excess male hormone levels. This complex disorder has both environmental influences, such as obesity and insulin resistance, and inappropriate endocrine signaling from the hypothalamus and pituitary glands as contributors. Hyperandrogenism presents clinically as hirsutism and acne and biochemically with elevated serum androgen levels. Androgen and androgen precursors can be produced and secreted by the ovaries and also by the adrenal cortices in about the same amount in response to stimulation by pituitary derived luteinizing hormone (LH) to the ovaries and adrenocorticotropic hormone (ACTH) to the adrenal gland, respectively. Emerging data indicate that PCOS patients can be categorized according to whether the source of excessive androgen is primarily from the ovaries, namely, functional ovarian hyperandrogenism (FOH), or the adrenal glands, namely, functional adrenal hyperandrogenism (FAH), both (FOH and FAH), or neither and attributable to either insulin resistance /obesity or of unknown origin. A majority or about two-thirds of cases have functionally typical PCOS (PCOS-T) that is due to typical FOH, characterized by hyperresponsiveness of 17-hydroxyprogesterone (17-OHP). About one fifth of cases have functionally atypical FOH (PCOS-A), lacking 17-OHP hyperresponsiveness. Within these two FOH populations, about one-third may have both FOH and FAH. About 8% of PCOS cases are attributed to either obesity and the remainder are unknown or idiopathic in nature. Only about 3-5% PCOS cases are due to isolated FAH with androgen responsiveness to ACTH.

## SUMMARY

**[0003]** Adrenal androgen excess in PCOS appears to occur independently of ovarian androgen excess, suggesting it may represent an intrinsic, and possible primary source of abnormal synthesis of adrenal androgens. Adrenal androgen excess of PCOS may not result from deficiencies in specific enzymatic steps, rather it may represent an altered pituitary responsivity to corticotropin releasing factor (CRF) and adrenocorticotropic hormone (ACTH).

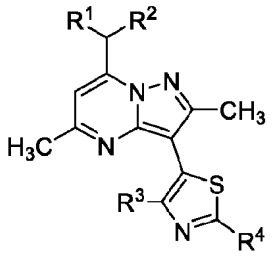
**[0004]** In an aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

**[0005]** In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

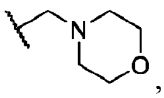
**[0006]** In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome (PCOS) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

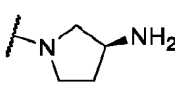
**[0007]** In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome (PCOS) in a subject in need thereof, comprising accessing a source of excessive androgen; and administering a CRF1 antagonist or pharmaceutically acceptable salt thereof. In some embodiments, the cosyntropin is administered at a dose about 1 $\mu g/m^2$. In some embodiments, the cosyntropin is administered at a dose about 10 $\mu g/m^2$. In some embodiments, the cosyntropin is administered at a dose about 250 $\mu g/m^2$. In some embodiments, the source of excessive androgen is adrenal glands. In some embodiments, the source of excessive androgen is ovaries.

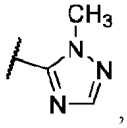
**[0008]** In some embodiments, the $CRF_1$ antagonist is a compound of Formula (I):

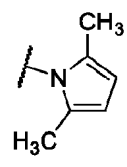



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein: $R^1$ and $R^2$ are independently ethyl or *n*-propyl; $R^3$ is hydrogen, F, Cl, Br, methyl, trifluoromethyl, or methoxy; $R^4$ is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, 

, 

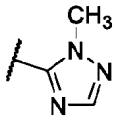
, 

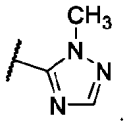
, or 

; $R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

**[0009]** In some embodiments, $R^3$ is F, Cl, Br, methyl, or trifluoromethyl.

**[0010]** In some embodiments, $R^3$ is Cl or Br.

**[0011]** In some embodiments, $R^4$ is $-NR^aR^b$, pyridin-4-yl, morpholin-4-yl, or .

**[0012]** In some embodiments, $R^4$ is morpholin-4-yl or .

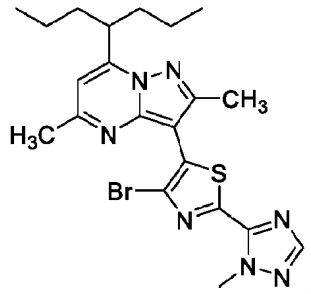
**[0013]** In some embodiments, $R^4$ is $-NR^aR^b$, and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

**[0014]** In some embodiments, the $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof is 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo[1,5-*a*]pyrimidine.

**[0015]** In some embodiments, the $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

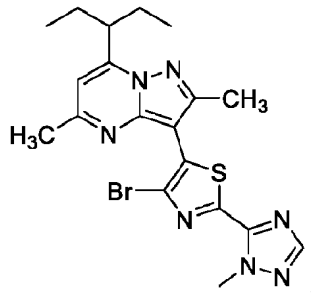
**[0016]** In some embodiments, the $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof is 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

**[0017]** In some embodiments, the $CRF_1$ antagonist is



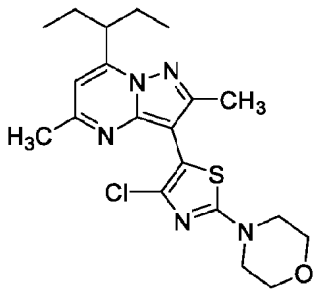
, or a pharmaceutically acceptable salt thereof.

**[0018]** In some embodiments, the $CRF_1$ antagonist is



, or a pharmaceutically acceptable salt thereof.

**[0019]** In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

**[0020]** In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SSR125543 (crinecerfont), and SN003.

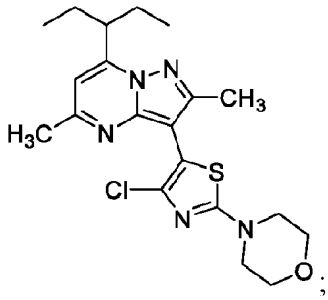
**[0021]** In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg to about 400 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 300 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 75 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

**[0022]** In some embodiments, an adrenocorticotropic hormone (ACTH) level is reduced by at least 5% from baseline. In some embodiments, an adrenocorticotropic hormone (ACTH) level is reduced by at least 10% from baseline. In some embodiments, a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 5% from baseline. In some embodiments, a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 10% from baseline. In some embodiments, the androstenedione (A4) level is reduced by at least 5% from baseline. In some embodiments, the androstenedione (A4) level is reduced by at least 10% from baseline. In some embodiments, the 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 5%

from baseline. In some embodiments, the 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 10% from baseline. In some embodiments, the 11β-hydroxytestosterone (11OHT) level is reduced by at least 5% from baseline. In some embodiments, the 11β-hydroxytestosterone (11OHT) level is reduced by at least 10% from baseline.

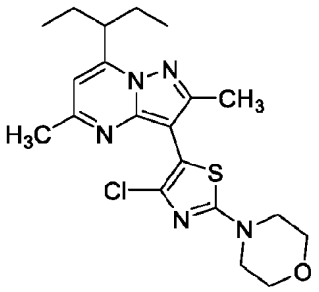
**[0023]** In some embodiments, a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 24 hours. In some embodiments, a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 4 weeks.

**[0024]** In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:



; or a pharmaceutically acceptable salt or solvate thereof.

**[0025]** In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH+FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:



; or a pharmaceutically acceptable salt or solvate thereof.

**[0026]** In some embodiments, the Compound 3 is administered at a dose between about 1 mg/day and about 400 mg/day.

**[0027]** In some embodiments, the pharmaceutical composition comprises about 25 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 75 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments,

the pharmaceutical composition comprises about 200 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 300 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

**[0028]** In some embodiments, the pharmaceutical composition is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm to about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μm.

**[0029]** In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule.

**[0030]** In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof. In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

**[0031]** In some embodiments, the subject is a pediatric patient. In some embodiments, the subject is from about 9 years old to about 18 years old. In some embodiments, the subject is from about 8 years of age to about 55 years of age. In some embodiments, the subject is an adult patient.

**[0032]** In some embodiments, the subject is treated for a period of about 2 weeks to about 36 weeks. In some embodiments, the subject is treated for a period of about 1 month to 12 months. In some embodiments, the subject is treated for a period of about 10 months to 50 years.

**[0033]** Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

## INCORPORATION BY REFERENCE

**[0034]** All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

## DETAILED DESCRIPTION

**[0035]** While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

**Polycystic Ovary Syndrome (PCOS)**

**[0036]** Polycystic ovarian syndrome (PCOS) is a heterogeneous disorder with multiple phenotypes and is one of the most common endocrine metabolic disorders in reproductive aged women. PCOS was first diagnosed and described as a syndrome of oligo-amenorrhea and polycystic ovaries that was variably accompanied by hirsutism, acne, and obesity. There are various diagnostic criteria for adolescent and adult patients considering the core diagnostic features, such as hyperandrogenism, persistent ovulatory dysfunction, and polycystic ovarian morphology (PCOM). The exact etiology of this disorder is not entirely clear, however, both genetic and environmental factors seem to play roles in causing the disorder. Generally, PCOS presents as a phenotype reflecting a self-perpetuating vicious cycle involving neuroendocrine, metabolic, and ovarian dysfunction and is characterized by excessive ovarian and/or adrenal androgen secretion. For example, intrinsic ovarian factors such as altered steroidogenesis and factors external to the ovary such as hyperinsulinemia contribute to the excessive ovarian androgen production. The classic ovarian phenotype of enlarged ovaries with string-of-pearl morphology and theca interstitial hyperplasia reflects androgen exposure; this morphology has also been observed in women with congenital adrenal hyperplasia (CAH).

**[0037]** In order to attempt to understand the pathophysiology of PCOS, it is important to understand the molecular basis of steroidogenesis and androgen source, production and physiology. Under normal circumstances in women, the ovaries and adrenal glands contribute about equally to testosterone production. Approximately half of testosterone originates from direct testosterone secretion by the ovaries and adrenal glands, whereas half is produced by

peripheral conversion of circulating androstenedione, which itself arises from approximately equal ovarian and adrenal secretion. Androgen production is not under direct negative feedback regulation by the neuroendocrine system in females, as is the case for estradiol and cortisol secretion. Androgens are secreted by both the ovaries and adrenal glands in response to their respective tropic hormones, LH and ACTH. The zona reticularis of the adrenal gland resembles the theca cell compartment of the ovary in its expression of the core enzymatic pattern for androgen production.

**[0038]** PCOS patients can be functionally categorized as distinct subtypes based on the source of androgen excess listed in Table 1 below. Androgen excess can be derived from the ovaries, the adrenal glands, both, or neither. Primary PCOS is the most common variety of PCOS without any known cause and a proposed theory suggests that functional ovarian hyperandrogenism (FOH) along with disturbance of hypothalamo-pituitary-ovarian (HPO) axis function may be the underlying cause. Further, functional adrenal hyperandrogenism (FAH) other than HPO axis disturbance may be explained for a certain population of PCOS patients. The PCOS patients with primary FAH may experience an average 50% increase in adrenal volume that correlates with hyperandrogenemia severity.

**[0039]** Table 1 Functional classification of PCOS based on source of androgen excess

| PCOS Functional Type | Source of Androgen | GnRHag Test 17OHP Response | DAST Testosterone Response | ACTH test DHEA Response | Prevalence Among PCOS |
|---|---|---|---|---|---|
| PCOS-T | Primary FOH (typical FOH) | High* | High in 92.5% | High in 28% (associated FAH) | 67%* |
| PCOS-A | Primary FOH (atypical FOH) | Normal* | High | High in 30% (associated FAH) | 20% |
| | Primary FAH (isolated FAH) | Normal | Normal | High | 5% |
| | PCOS without FOH or FAH (PCOS-A of obesity or idiopathic PCOS-A) | Normal | Normal | Normal | 8% |

**[0040]** Test procedures to determine the source of androgen are listed below in Table 2. The ovarian hyperandrogenism of PCOS is demonstrated directly by the GnRHag test or the hCG test and in combination with the dexamethasone androgen-suppression test (DAST). The GnRHag test determines the coordinated function of the ovarian follicle. Leuprolide acetate 10 µg/kg sc (or a comparable dose of any other short-acting GnRHag) stimulates endogenous LH and FSH release that peaks at 3–4 hours and persists for 24 hours; this in turn stimulates increased secretion of sex steroids and their precursors, with serum levels peaking at 18–24 hours. In the absence of evidence of a steroidogenic block, an elevated 17OHP response is typical of PCOS. Ovarian steroidogenic enzyme deficiency, which is rare, can be detected by an abnormal pattern of steroid intermediates in response to the test. hCG is an LH analog: 5000 IU intramuscularly stimulates steroidogenic responses comparable with those of a GnRHag test at 24 hours. DAST indirectly tests for ovarian source of androgens by suppressing ACTH-dependent androgen production of androgens. In the presence of normal adrenocortical

suppression an inappropriately elevated serum testosterone post-DAST indicates an ACTH-independent source of androgen, which is ordinarily of ovarian origin.

**[0041]** Adrenal hyperandrogenism may be demonstrated by a rapid ACTH test: cosyntropin is administered iv and peak steroid responses occur at 15–60 minutes. An elevated DHEA post this test indicates an ACTH-dependent source of androgen, which is ordinarily of adrenal origin. The test may be performed using cosyntropin 250 μg, this is a supramaximal dose. Lower doses of cosyntropin may be used (10 μg/m2) which elicit a similar peak response. A low-dose ACTH test (1.0-μg cosyntropin) may be used and may be more physiologic. It usually elicits nearly as great a peak response that promptly wanes, and in PCOS, does not elicit such a wide spectrum of elevated steroid intermediates as do larger doses.

**[0042]** Table 2 Methods to determine source of female androgen excess

| Test | Rationale | Method | Outcome Measures | Interpretation* |
|---|---|---|---|---|
| GnRHag | Endogenous LH and FSH release stimulates coordinated function of ovarian follicles | Leuprolide acetate 10 μg/kg sc (for maximum stimulation) | Ovarian steroid secretion peaks at 20–24 h | 17OHP >152 ng/dL without steroidogenic block indicates typical FOH (PCOS-T) |
| hCG | Exogenous administration of LH analog stimulates theca-interstitial cells | hCG 3000 IU/m² (for maximum stimulation) | Ovarian steroid secretion peaks at 24 h | 17OHP >152 ng/dL without steroidogenic block indicates typical FOH (PCOS-T) |
| LDAST | Long DAST: dexamethasone profoundly suppresses adrenal androgens over several days | Dexamethasone 0.5 mg OID per os × 4–5 d | Free testosterone, DHEAS, cortisol; sample early morning d 5 | Free testosterone ≥8 pg/mL with DHEAS <70 and cortisol <1 μg/dL characteristic of FOH |
| SDAST | Short DAST: dexamethasone rapidly suppresses adrenal testosterone and cortisol | Dexamethasone 0.25 mg/m² per os at 12 noon | Total testosterone, cortisol, sample 4 PM (4 h) | Total testosterone >26 ng/mL, cortisol <5 μg/dL suggests FOH |
| ACTH | Exogenous ACTH stimulates adrenal steroidogenesis | Cosyntropin ≥10 μg/m² (for maximum stimulation) | DHEA,17OHP, steroid intermediates, cortisol peak at 30–60 min | DHEA 1500–3000 μg/dL without steroidogenic block indicates FAH |

**Corticotropin releasing factor**

**[0043]** Currently, no single universal treatment for PCOS is available. As a result, current treatments tend to be individualized and adapted to the actual needs of the individual patient. Furthermore, treatment may be symptom-oriented. For example, targets for pharmacological treatment may include androgen excess. For PCOS patients with elevated adrenal androgens, FOH+FAH and PCOS-FAH patients, in some embodiments, pharmacological treatment, such as corticotropin releasing factor (CRF) receptor antagonist targeting ACTH production may be used.

**[0044]** Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of

autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

**[0045]** CRF has been implicated in psychiatric disorders and neurological diseases including depression and anxiety, as well as the following: Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol and substance abuse and associated withdrawal symptoms, obesity, metabolic syndrome, congenital adrenal hyperplasia (CAH), Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulceration, premenstrual syndrome, sexual dysfunction, premature labor, inflammatory disorders, allergies, multiple sclerosis, visceral pain, sleep disorders, pituitary tumors or ectopic pituitary derived tumors, chronic fatigue syndrome, and fibromyalgia.

**[0046]** CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotropic hormone ("ACTH"), β-endorphin, and other proopiomelanocortin ("POMC")-derived peptides from the anterior pituitary. Secretion of CRF causes release of ACTH from corticotrophs in the anterior pituitary via binding to the $CRF_1$ receptor, a member of the class B family of G-protein coupled receptors.

**[0047]** Due to the physiological significance of $CRF_1$, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the $CRF_1$ receptor remains a desirable goal and has been the subject of ongoing research and development for the treatment of anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse, and congenital adrenal hyperplasia.

**[0048]** The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. The middle layer, the zona reticularis is responsible for the production of androgens such as DHEA, DHEAS and androstenedione, (A4) the precursor to testosterone (T) and dihydrotestosterone (DHT). This layer is also responsible for the production of the 11-oxyandrogens, 11β-hydroxyandrostenedione (11OHA4) and 11β-hydroxytestosterone (11OHT), which are major bioactive androgens, particularly in women. Due to an unknown cause in PCOS patients with elevated androgens, the zone reticularis displays a hyperresponsiveness to ACTH resulting excessive levels of DHEA, DHEAS, 11OHA4, 11OHT and A4. The excessive ACTH stimulation causes hypertrophy of the zona reticularis resulting in

adrenal hyperplasia and clinically manifests with physical features typical of PCOS and hyperandrogenism. Reducing the stimulatory effect on the pituitary's ACTH secretion by inhibiting the CRF1 receptor is expected is reduce excessive androgen synthesis from the ACTH responsive zone of the adrenal gland in PCOS. The normalization of elevated androgen levels in the short term would be expected to ameliorate cardinal features of PCOS - hirsutism, acne and menstrual irregularities – over the long term.

**Certain Definitions**

**[0049]** Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

**[0050]** As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

**[0051]** The term "about" is used to indicate that a value includes 10% level of error for the device or method being employed to determine the value.

**[0052]** The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or."

**[0053]** "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, and preferably having from one to five carbon atoms (i.e. $C_1$-$C_5$alkyl). In some embodiments, an alkyl comprises one to four carbon atoms (i.e., $C_1$-$C_4$alkyl). ). In some embodiments, an alkyl comprises one to three carbon atoms (i.e., $C_1$-$C_3$alkyl). ). In some embodiments, an alkyl comprises one to two carbon atoms (i.e., $C_1$-$C_2$alkyl). In some embodiments, an alkyl comprises one carbon atom (i.e., $C_1$alkyl). In certain embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (iso-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (sec-butyl), 2-methylpropyl (isobutyl), 1,1-dimethylethyl (tert-butyl), or 1-pentyl (n-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more substituents such as those described herein.

**[0054]** The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises,"

"has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

**[0055]** "Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. "Administering" a pharmaceutical composition may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

**[0056]** By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

**[0057]** The term "pharmaceutical composition" means a composition comprising at least one active ingredient, such as a steroid or a pharmaceutically acceptable salt thereof or a $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

**[0058]** The term "supraphysiologic amount" describes glucocorticoid dose levels that are above the daily glucocorticoid requirement (production rate) found in healthy individuals.

**[0059]** The term "physiologic amount" describes glucocorticoid dose levels that meet the daily glucocorticoid requirement (production rate) found in healthy individuals.

**[0060]** The term "hydrocortisone equivalents" as used herein is understood by a person skilled in the art to be the conversion calculations needed to be considered when substituting one glucocorticoid for another as the potency and duration of action of various glucocorticoids may vary. Hence, the term "hydrocortisone equivalents" is the standard used for comparison of glucocorticoid potency.

**[0061]** A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the

pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

**[0062]** The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

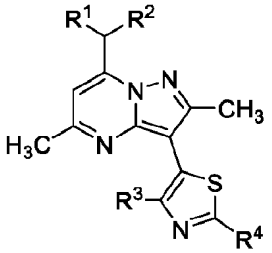
**Compounds**

**[0063]** Disclosed herein are $CRF_1$ antagonists or pharmaceutically acceptable salt thereof such as Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003, and SSR125543 (crinecerfont).

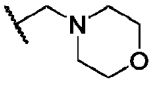
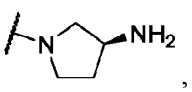
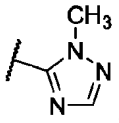
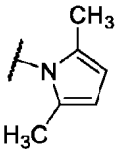
**[0064]** In one aspect, the $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: *n*-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine hydrochloride (Antalarmin hydrochloride), *n*-butyl-N-ethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine hydrochloride (Pfizer CP154526), N-(1-Ethylpropyl)-3,6-dimethyl-2-(2,4,6-trimethylphenox y)-4-pyridinamine hydrochloride (Pfizer CP376395 hydrochloride), 5-Chloro-N-(cyclopropylmethyl)-2-methyl-*n*-propyl-N'-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride (NBI27914 hydrochloride), (7S)-6-(Cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene hydrochloride (NBI35965 hydrochloride), N-(1-Ethylpropyl)-3-methoxy-5-[2-methoxy-4-

(trifluoromethoxy)phenyl]-6-methyl-2-pyrazinamine hydrochloride (NGD 98-2 hydrochloride), 8-(6-Methoxy-2-methyl-3-pyridinyl)-2,7-dimethyl-N-[(1R)-1-methylpropyl]pyrazolo[1,5-a]-1,3,5-triazin-4-amine (Pexacerfont), 3-[6-(Dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-a]pyrimidin-7-amine hydrochloride (R 121919 hydrochloride), and N-(4-Methoxy-2-methylphenyl)-1-[1-(methoxymethyl)propyl]-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridine-4-amine (SN003), (S)-4-(2-chloro-4-methoxy-5-methylphenyl)-N-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-(prop-2-yn-1-yl)thiazol-2-amine (SSR125543).

**[0065]** Disclosed herein is a compound of Formula (I):



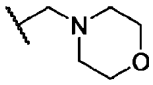
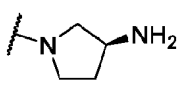
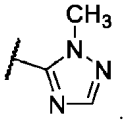
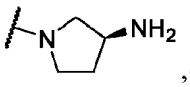
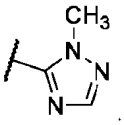
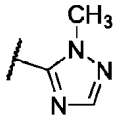
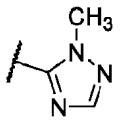
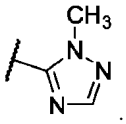
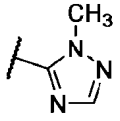
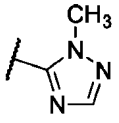
Formula (I)

or a pharmaceutically acceptable salt thereof, wherein $R^1$ and $R^2$ are independently ethyl or *n*-propyl; $R^3$ is H, Cl, Br, methyl, trifluoromethyl, or methoxy; $R^4$ is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and

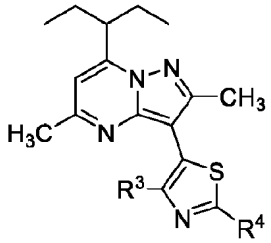
$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

**[0066]** In some embodiments, $R^1$ and $R^2$ are independently ethyl or *n*-propyl. In some embodiments, $R^1$ is ethyl and $R^2$ is *n*-propyl. In some embodiments, $R^1$ is *n*-propyl and $R^2$ is ethyl. In some embodiments, $R^1$ and $R^2$ are both ethyl. In some embodiments, $R^1$ and $R^2$ are both *n*-propyl.

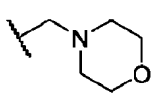
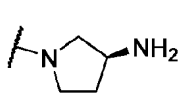
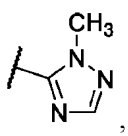
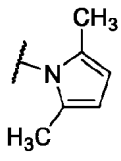
**[0067]** In some embodiments, $R^3$ is hydrogen, Cl, Br, methyl, or trifluoromethyl. In some embodiments, $R^3$ is hydrogen, Cl, Br, or methyl. In some embodiments, $R^3$ is hydrogen, Cl, or Br. In some embodiments, $R^3$ is hydrogen. In some embodiments, $R^3$ is Cl. In some embodiments, $R^3$ is Br.

**[0068]** In some embodiments, $R^4$ is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , ,or . In some embodiments, $R^4$ is Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, ,or . In some embodiments, $R^4$ is $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or . In some embodiments, $R^4$ is $-NR^aR^b$, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or . In some embodiments, $R^4$ is $-NR^aR^b$,pyridin-4-yl, morpholin-4-yl, or . In some embodiments, $R^4$ is morpholin-4-yl or . In some embodiments, $R^4$ is morpholin-4-yl. In some embodiments, $R^4$ is . In some embodiments, $R^4$ is $-NR^aR^b$ and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

**[0069]** Disclosed herein is a compound of Formula (II):

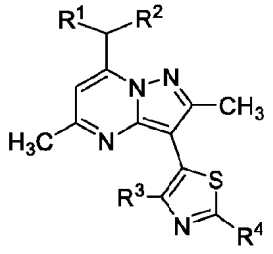


Formula (II)

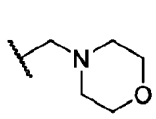
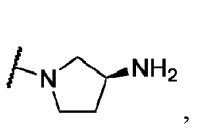
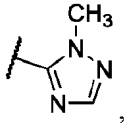
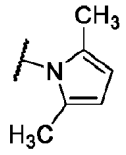
or a pharmaceutically acceptable salt thereof, wherein $R^3$ is H, Cl, Br, methyl, trifluoromethyl, or methoxy; $R^4$ is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and $R^a$ and $R^b$ are independently

hydrogen, $C_1$-$C_3$alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$–$CH_2CH_2NHCH_2CH_2CH_3$.

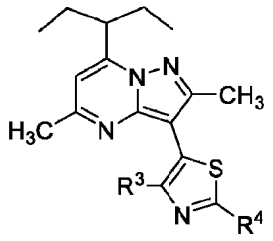
**[0070]** Disclosed herein is a compound of Formula (III):



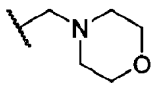
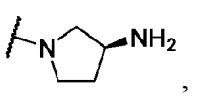
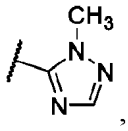
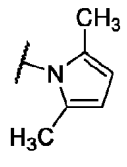
Formula (III)

or a pharmaceutically acceptable salt thereof, wherein $R^1$ and $R^2$ are *n*-propyl; $R^3$ is H, Cl, Br, methyl, trifluoromethyl, or methoxy; $R^4$ is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and $R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

**[0071]** Disclosed herein is a compound of Formula (IV):

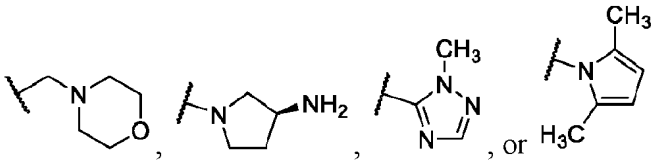
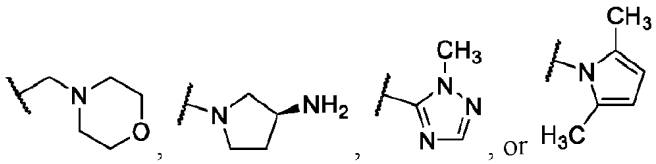
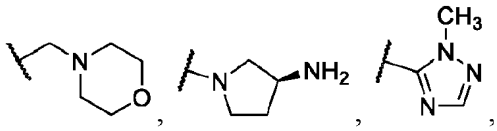
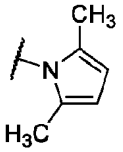
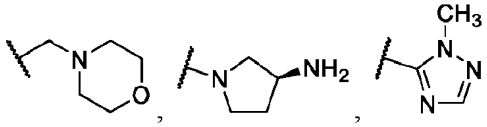
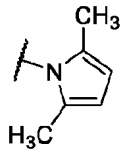
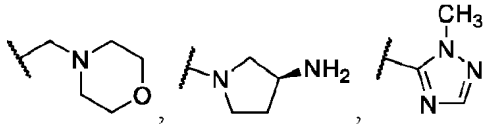


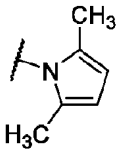
Formula IV

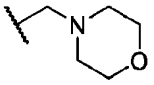
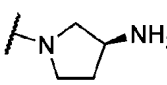
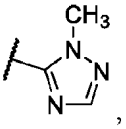
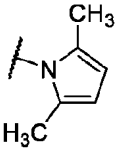
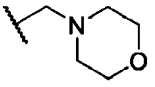
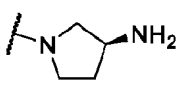
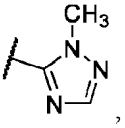
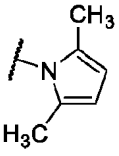
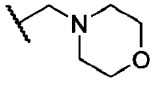
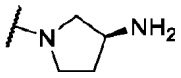
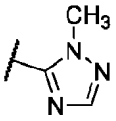
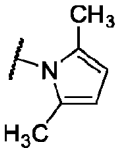
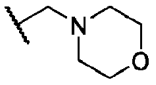
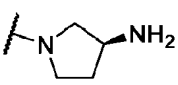
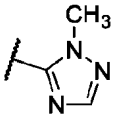
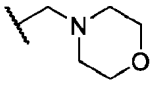
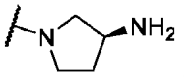
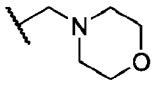
or a pharmaceutically acceptable salt thereof, wherein $R^3$ is Cl, Br, methyl, trifluoromethyl, or methoxy; $R^4$ is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and $R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

**[0072]** For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^3$ may be hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^3$ may be Cl, Br, methyl, trifluoromethyl, or methoxy. For a compound or pharmaceutically acceptable salt of Formula

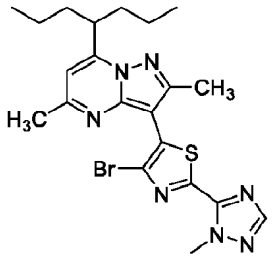
(I), (II), (III), and (IV), $R^3$ may be Cl, Br, methyl, or trifluoromethyl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^3$ may be Cl, Br, or methyl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^3$ may be Cl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^3$ may be Br. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^3$ may be methyl.

**[0073]** For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is Br, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is Br, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is Br, acetamido, pyridin-4-yl, morpholin-4-yl, , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is Br, pyridin-4-yl, morpholin-4-yl, , or



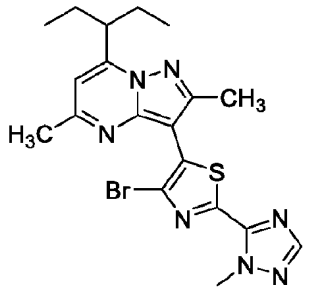
. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is pyridin-4-yl, morpholin-4-yl, , , , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is morpholin-4-yl, , , , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is , , , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is , , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), $R^4$ is morpholin-4-yl.

**[0074]** Disclosed herein is 3-[4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]pyrimidine (Compound 1) or a pharmaceutically acceptable salt thereof:



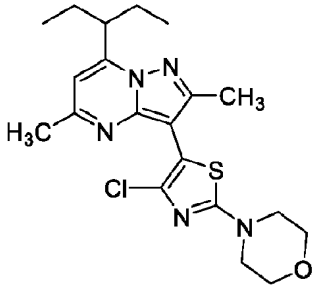
Compound 1.

**[0075]** Disclosed herein is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (Compound 2) or a pharmaceutically acceptable salt thereof:



Compound 2.

**[0076]** Disclosed herein is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine (or alternatively 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine) (Compound 3) or a pharmaceutically acceptable salt thereof:



Compound 3.

**[0077]** In some embodiments, 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine is referred to as Compound 3. In some embodiments, 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine is referred to as Compound 3.

**[0078]** In one aspect, the $CRF_1$ antagonist or pharmaceutically acceptable salt thereof may be an astressin. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

**Pharmaceutical Compositions**

**[0079]** Disclosed herein are pharmaceutical compositions comprising a compound or pharmaceutically acceptable salt described herein. In certain embodiments, the composition comprises a steroid or a pharmaceutically acceptable salt thereof and a $CRF_1$ antagonist or pharmaceutically acceptable salt thereof as disclosed above. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is exogenous glucocorticoids (GC) or a pharmaceutically acceptable salt thereof.

*Dosage Form*

**[0080]** In some embodiments, the pharmaceutical compositions described herein are provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound or pharmaceutically acceptable salt described herein that is suitable for administration to an animal, preferably mammal, subject in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

**[0081]** Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

**[0082]** In some embodiments, the pharmaceutical compositions described herein are formulated as oral dosage forms. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules. In some embodiments, the pharmaceutical composition comprises one or more additional pharmaceutically acceptable excipients. See, e.g., Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005) for a list of pharmaceutically acceptable excipients.

*Capsule*

**[0083]** In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

**[0084]** In some embodiments, the capsule is formed using materials which include, but are not limited to, natural or synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, or any combinations thereof. In some embodiments, the capsule is formed using preservatives, coloring and opacifying agents,

flavorings and sweeteners, sugars, gastroresistant substances, or any combinations thereof. In some embodiments, the capsule is coated. In some embodiments, the coating covering the capsule includes, but is not limited to, immediate release coatings, protective coatings, enteric or delayed release coatings, sustained release coatings, barrier coatings, seal coatings, or combinations thereof. In some embodiments, a capsule herein is hard or soft. In some embodiments, the capsule is seamless. In some embodiments, the capsule is broken such that the particulates are sprinkled on soft foods and swallowed without chewing. In some embodiments, the shape and size of the capsule also vary. Examples of capsule shapes include, but are not limited to, round, oval, tubular, oblong, twist off, or a non-standard shape. The size of the capsule may vary according to the volume of the particulates. In some embodiments, the size of the capsule is adjusted based on the volume of the particulates and powders. Hard or soft gelatin capsules may be manufactured in accordance with conventional methods as a single body unit comprising the standard capsule shape. A single-body soft gelatin capsule typically may be provided, for example, in sizes from 3 to 22 minims (1 minims being equal to 0.0616 ml) and in shapes of oval, oblong or others. The gelatin capsule may also be manufactured in accordance with conventional methods, for example, as a two-piece hard gelatin capsule, sealed or unsealed, typically in standard shape and various standard sizes, conventionally designated as (000), (00), (0), (1), (2), (3), (4), and (5). The largest number corresponds to the smallest size. In some embodiments, the pharmaceutical composition described herein (e.g., capsule) is swallowed as a whole.

**[0085]** In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients. In some embodiments, the capsule is free of additional excipients.

**[0086]** In some embodiments, a capsule is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the capsule has a dose strength of up to 200 mg. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus II.

***Tablet***

**[0087]** Poorly soluble drugs may be difficult to formulate using standard technologies such as high shear wet granulation. Optimum delivery of poorly soluble drugs may require complex technologies such as solid solutions amorphous dispersions (hot melt extrusion or spray drying), nano-formulations or lipid-based formulations. Hydrophobic drug substances may be considered poorly soluble according to USP criteria and may be known to be difficult to granulate with water and other excipients. This is likely due to most known excipients for

immediate release formulations being water soluble or water-swellable. Making a tablet of a high dose drug substance that is poorly soluble may require a high concentration of the drug substance. However, as the drug concentration is increased above a certain level, formation of granules may become more and more difficult. Furthermore, at a certain drug load, it may become impossible.

**[0088]** In some embodiments, the pharmaceutical composition is formulated as a tablet.

**[0089]** In some embodiments, the tablet is made by compression, molding, or extrusion, optionally with one or more pharmaceutically acceptable excipient. In some embodiments, compressed tablets are prepared by compressing a compound or pharmaceutically acceptable salt described herein in a free-flowing form, optionally mixed with pharmaceutically acceptable excipients. In some embodiments, molded tablets are made by molding a mixture of the powdered a compound or pharmaceutically acceptable salt described herein, moistened with an inert liquid diluent. In some embodiments, the tablet is prepared by hot-melt extrusion. In some embodiments, extruded tablets are made by forcing a mixture comprising a compound or pharmaceutically acceptable salt described herein, through an orifice or die under controlled conditions. In some embodiments, the tablet is coated or scored. In some embodiments, the tablet is formulated so as to provide slow or controlled release of a compound or pharmaceutically acceptable salt described herein. In some embodiments, a tablet is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the tablet has a dose strength of up to 200 mg. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus II.

**[0090]** In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg, less than about 200 mg, less than about 100 mg or less than 50 mg. In some embodiments, the tablet has a dose strength of more than about 10 mg, more than about 50 mg, more than about 100 mg, more than about 150 mg, more than about 200 mg, or more than about 250 mg. In some embodiments, the tablet size is less than about 1000 mg for a dose strength of more than about 50 mg. In some embodiments, the tablet size is less than 800 mg for a dose strength of more than about 100 mg. In some embodiments, the tablet size is less than 600 mg for a dose strength of more than about 150 mg. In some embodiment, the tablet size is less than 400 mg for a dose strength of more than about 200 mg. In some embodiments, the tablet size is less than 400 mg for a dose strength of 100 mg. In some

embodiments, the tablet size is less than 200 mg for a dose strength of 50 mg. In some embodiments, the tablet size is less than 50 mg for a dose strength of 10 mg.

**[0091]** In some embodiments, more than about 20% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 24 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 12 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 6 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 3 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 2 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 90% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 100% of the tablet is dissolved in less than 60 minutes in conventional dissolution media.

**[0092]** In some embodiments, the tablet is produced at a commercial scale.

**[0093]** In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

**[0094]** In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete dry

powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone, polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

***Pharmaceutically Acceptable Excipients***

**[0095]** In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient. In some embodiments, the composition is free of pharmaceutically acceptable excipients. The term "pharmaceutically acceptable excipient", as used herein, means one or more compatible solid or encapsulating substances, which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction, which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. In some embodiments, the pharmaceutically acceptable excipient is of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal, being treated.

**[0096]** Some examples of substances, which can serve as pharmaceutically acceptable excipients include:

- Amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, the amino acid is arginine. In some embodiments, the amino acid is L-arginine.
- Monosaccharides such as glucose (dextrose), arabinose, mannitol, fructose (levulose), and galactose.
- Cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose.

- Solid lubricants such as talc, stearic acid, magnesium stearate, and sodium stearyl fumarate.
- Polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol.
- Emulsifiers such as the polysorbates.
- Wetting agents such as sodium lauryl sulfate, Tween®, Span , alkyl sulphates, and alkyl ethoxylate sulphates.
- Diluents such as calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose.
- Binders such as starches (corn starch and potato starch), gelatin, sucrose, hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC).
- Disintegrants such as starch, and alginic acid.
- Super-disintegrants such as ac-di-sol, croscarmellose sodium, sodium starch glycolate and crospovidone.
- Glidants such as silicon dioxide.
- Coloring agents such as the FD&C dyes.
- Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors.
- Preservatives such as benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate, phenylmercuric nitrate, parabens, and sodium benzoate.
- Tonicity adjustors such as sodium chloride, potassium chloride, mannitol, and glycerin.
- Antioxidants such as sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA.
- pH adjuster such as NaOH, sodium carbonate, sodium acetate, HCl, and citric acid.
- Cryoprotectants such as sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran.
- Cationic surfactants such as cetrimide, benzalkonium chloride and cetylpyridinium chloride.
- Anion surfactants such as alkyl sulphates, alkyl ethoxylate sulphates, soaps, carboxylates, sulfates, and sulfonates.
- Non-ionic surfactants such as polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glyol

esters, glycerol esters, sorbitan derivatives, polyethylene glycol (PEG-40, PEG-50, PEG-55), and ethers of fatty alcohols.

- Organic materials such as carbohydrate and modified carbohydrates, lactose, a-lactose monohydrate, spray dried lactose and anhydrous lactose, starch and pre-gelatinized starch, sucrose, manitol, sorbitol, cellulose, powdered cellulose and microcrystalline cellulose.
- Inorganic materials such as calcium phosphates (anhydrous dibasic calcium phosphate, dibasic calcium phosphate and tribasic calcium phosphate).
- Co-processed diluents.
- Surfactants such as sodium lauryl sulfate.
- Compression aids.
- Anti-tacking agents such as silicon dioxide and talc

***Amounts***

**[0097]** In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 400 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 300 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 200 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 100 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 90 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 80 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 70 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 60 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 50 mg of a compound or pharmaceutically acceptable salt

described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 40 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 30 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 20 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 10 mg of a compound or pharmaceutically acceptable salt described herein.

**[0098]** In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 200 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 100 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 90 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 80 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 70 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 60 mg of a compound or pharmaceutically acceptable salt described herein f. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 50 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 40 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg

and about 30 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 20 mg of a compound or pharmaceutically acceptable salt described herein.

***Particle size***

**[0099]** In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises a compound or pharmaceutically acceptable salt described herein, in the form of microparticles. In some embodiments, the microparticles have an average size from about 1 μm to about 100 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 50 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 30 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 20 μm. In some embodiments, the microparticles have an average size from about 5 μm to about 15 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 10 μm. In some embodiments, the microparticles have an average size from about 3 μm to about 10 μm. In some embodiments, the microparticles have an average size from about 4 μm to about 9 μm.

**Methods of Treatment**

**[0100]** Disclosed herein are methods of treating polycystic ovary syndrome (PCOS) in a subject in need thereof, comprising administering a compound or pharmaceutically acceptable salt described herein. In some embodiments, the subject in need thereof has PCOS-FAH. In some embodiments, the subject in need thereof has PCOS-FOH+FAH. In some embodiments, the methods described herein result in the reduction of a level of a hormone. Such hormones include deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, 17-OHP, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEAS), androstenediol, androstenedione (A4), testosterone (T), dihydrotestosterone (DHT), estrone, estradiol, estriol, 11β-hydroxyandrostenedione (11OHA4), 11β-hydroxytestosterone (11OHT), 11-ketoandrostenedione (11KA4), 11-ketotestosterone (11KT), 11β-hydroxy-5α-androstenedione (11OHDHA4), 11-keto-5α-androstenedione (11KDHA4), 11β-hydroxydihydrotestosterone (11OHDHT), 11-ketodihydrotestosterone (11KDHT) and ACTH. In some embodiments, the methods described herein result in the reduction of 17-OHP levels. In some embodiments, the methods described herein result in the reduction of A4 levels. In some embodiments, the methods described herein result in the reduction of ACTH levels. In some embodiments, the methods described herein result in the reduction of DHEA levels. In some embodiments, the methods described herein result in the reduction of DHEAS levels. In some embodiments, the methods described herein

result in the reduction of testosterone (T) levels. In some embodiments, the methods described herein result in the reduction of DHT levels. In some embodiments, the methods described herein result in the reduction of 11OHA4 levels. In some embodiments, the methods described herein result in the reduction of 11OHT levels. In some embodiments, the methods described herein result in the reduction of 11KA4 levels. In some embodiments, the methods described herein result in the reduction of 11KT levels.

**[0101]** Further, in some embodiments, the methods described herein result in the maintenance of the reduction of 17-OHP, A4, ACTH, DHEA, DHEAS, T, DHT, 11OHA4, 11OHT, 11KA4,and/or 11KT levels. In some embodiments, the reductions of 17-OHP, A4, ACTH, DHEA, DHEAS, T, DHT, 11OHA4, 11OHT, 11KA4 and/or 11KT levels may last for at least 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 2 years, 5 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years, or 100 years.

**[0102]** In some embodiments, the methods described herein result in the reduction of DHEAS levels. In some embodiments, the DHEAS level is reduced by at least about 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% from baseline. The baseline level of the DHEAS may be measured in a subject before beginning the treatment disclosed herein. In some embodiments, the DHEAS level is reduced by at least 5% from baseline. In some embodiments, the reduced DHEAS level from baseline may be maintained for at least about 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 48 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, or 30 weeks.

**[0103]** Further, in some embodiments, the methods described herein result in the maintenance of the reduction of 17-OHP, A4, ACTH, T, DHT, 11OHA4, 11OHT, 11KA4 and/or 11KT levels. In some embodiments, the reductions of 17-OHP, A4, ACTH T, DHT, 11OHA4, 11OHT, 11KA4 and/or 11KT levels may last for at least 24 hours, 36 hours, 48 hours, 60 hours, 72

hours, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 2 years, 5 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years, or 100 years.

**[0104]** In some embodiments, disclosed herein are methods for treating PCOS in a subject in need thereof, and the methods further comprise accessing a source of excessive androgen; and administering a $CRF_1$ antagonist or pharmaceutically acceptable salt thereof. In some embodiments, accessing a source of excessive androgen comprises measuring the primary source of excessive androgen produced in the subject suffering PCOS. In some embodiments, the primary source is the ovaries. In some embodiments, the primary source is the adrenal glands. In some embodiments, the primary source is both the ovaries and the adrenal glands. In some embodiments, the primary source is an organ that is able to produce androgen.

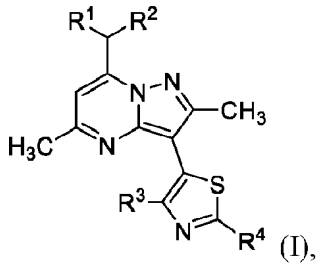
**[0105]** In some embodiments, cosyntropin or any other suitable hormones or chemical compounds may be administered to a subject for ACTH response in order to test for adrenal hyperandrogenism. In some embodiments, the cosyntropin is administered at a dose at least about 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 250or $\mu g/m^2$. In some embodiments, the cosyntropin is administered at a dose at about the range between the doses disclosed herein. In some embodiments, the cosyntropin is administered at a dose at most about 250, 200, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, 5, 4, 3, 2, 1 $\mu g/m^2$.

**[0106]** In some embodiments, the subject will be treated for a period of about 1 week to about 40 weeks. In some embodiments, the subject will be treated for a period of about 2 weeks to about 39 weeks. In some embodiments, the subject will be treated for a period of about 3 weeks to about 38 weeks. In some embodiments, the subject will be treated for a period of about 4 weeks to about 36 weeks. In some embodiments, the subject will be treated for a period of about 1 month to 12 months. In some embodiments, the subject will be treated for a period of about 10 months to 10 years. In some embodiments, the subject will be treated for a period of about 1 months to 10 years. In some embodiments, the subject will be treated for a period of about 10 months to 20 years. In some embodiments, the subject will be treated for a period of about 1 months to 20 years. In some embodiments, the subject will be treated for a period of about 10

months to 30 years. In some embodiments, the subject will be treated for a period of about 1 months to 30 years. In some embodiments, the subject will be treated for a period of about 10 months to 40 years. In some embodiments, the subject will be treated for a period of about 1 months to 40 years. In some embodiments, the subject will be treated for a period of about 10 months to 50 years. In some embodiments, the subject will be treated for a period of about 1 months to 50 years.

**[0107]** In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SSR125543 (crinecerfont), AND SN003.

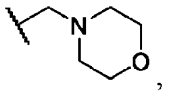
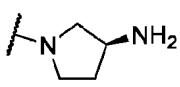
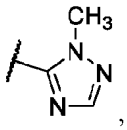
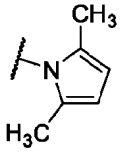
**[0108]** In some embodiments, the $CRF_1$ antagonist is a compound of Formula (I):


(I),

or a pharmaceutically acceptable salt thereof, wherein:

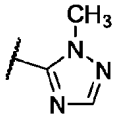
$R^1$ and $R^2$ are independently ethyl or *n*-propyl;

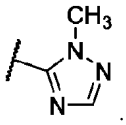
$R^3$ is hydrogen, F, Cl, Br, methyl, trifluoromethyl, or methoxy; and

$R^4$ is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and

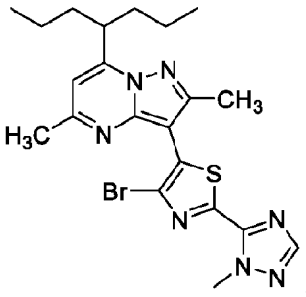
$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$–$CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$–.

**[0109]** In some embodiments, $R^3$ is F, Cl, Br, methyl, or trifluoromethyl. In some embodiments, $R^3$ is Cl, Br, or methyl.

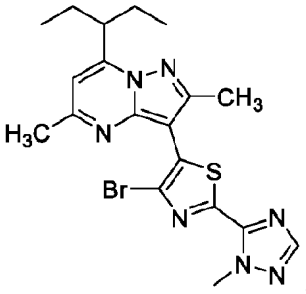
**[0110]** In some embodiments, $R^4$ is Br, $-NR^aR^b$–$NR^aR^b$, pyridin-4-yl, morpholin-4-yl, or . In some embodiments, $R^4$ is morpholin-4-yl or


. In some embodiments, $R^4$ is hydrogen, Br, $-NR^aR^b$ and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

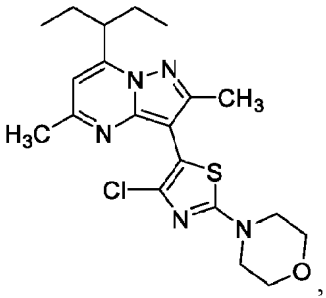
**[0111]** In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

**[0112]** In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

**[0113]** In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

**[0114]** In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg to about 200 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

**[0115]** In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is

administered in a dose of about 40 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 30 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 20 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 15 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject. In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg total daily dose to the subject.

**[0116]** In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm to about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μ.

**[0117]** In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

**[0118]** In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

**[0119]** In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

**[0120]** In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 1 to about 8 hours in a subject. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 to about 7 hours in a subject. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or

a tablet as to provide a Tmax of about 2 to about 6 hours in a subject. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 3 to about 5 hours in a subject.

**[0121]** In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 8 hours in a subject. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 7 hours in a subject. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 6 hours in a subject. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 5 hours in a subject. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 4 hours in a subject. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 3 hours in a subject. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 hours in a subject. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 1 hour in a subject.

**[0122]** In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof once a month, twice a month, three times a month, once a week, twice a week, three times a week, once every two days, once a day, twice a day, three times a day, or four times a day. In some embodiments, the methods described herein administer $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof twice a day.

**[0123]** In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, $CRF_1$ antagonist or pharmaceutically acceptable salt is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1500 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1400 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1300

mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1100 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 900 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 60 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 70 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 80 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 90 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 100 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 100 mg/day and about 700 mg/day. In some embodiments, Compound 3 is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 3 is administered at a dose between 150 mg/day and about 600 mg/day. In some embodiments, Compound 3 is administered at a dose between 200 mg/day and about 600 mg/day. In some embodiments, Compound 3 is administered at a dose between 200 mg/day and about 500 mg/day. In some embodiments, Compound 3 is administered at a dose between 200 mg/day and about 400 mg/day. In some embodiments, Compound 3 is administered at a dose between 25 mg/day and about 200 mg/day.

**[0124]** In some embodiments, Compound 3 is administered at a dose of about 500 mg/day. In some embodiments, Compound 3 is administered at a dose of about 400 mg/day. In some embodiments, Compound 3 is administered at a dose of about 300 mg/day. In some embodiments, Compound 3 is administered at a dose of about 200 mg/day. In some embodiments, Compound 3 is administered at a dose of about 150 mg/day. In some embodiments, Compound 3 is administered at a dose of about 100 mg/day. In some embodiments, Compound 3 is administered at a dose of about 50 mg/day.

**[0125]** In some embodiments, about 50 mg to about 1600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 1600 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of $CRF_1$

antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 800 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 600 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt is administered per day. In some embodiments, about 300 mg to about 600 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

**[0126]** In some embodiments, less than about 2000 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1200 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1000 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 800 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some

embodiments, less than about 600 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 500 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 400 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 300 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 200 mg $CRF_1$ antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day.

**[0127]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein wherein the subject is in the fed state. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein wherein the subject is in the fasted state.

**[0128]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

**[0129]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 4 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 3 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 2 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 1 hour before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 30 mins before sleep.

**[0130]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

**[0131]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 11 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 10 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 9 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 8 pm at night.

**[0132]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in combination with eflornithine and/or retinoids. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in combination with contraceptive pills containing androgen receptor blockers such as cyproterone acetate, spironolactone, flutamide, or 5α-reductase inhibitors.

**[0133]** In some embodiments, the levels of DHEA, DHEAS, A4, 11OHA4, T, 11OHT, DHT and/or ACTH in the subject are determined from a biological sample from the subject. In some embodiments, the biological sample is selected from the group of blood, blood fractions, plasma, serum, urine, other types of bodily secretions, and saliva. In some embodiments, the biological sample is obtained non-invasively.

**[0134]** In some embodiments, the subject is a pediatric patient. In some embodiments, the subject is an adolescent. In some embodiments, the subject is from about 8 years old to about 18 years old. In some embodiments, the subject is an adult patient. In some embodiments, the subject is from about 18 years old to about 55 years old. In some embodiments, the subject is from about 18 years old to about 50 years old.

**[0135]** In some embodiments, the steroid and the $CRF_1$ antagonist are administered concurrently. In some embodiments, the steroid and the $CRF_1$ antagonist are administered in one pharmaceutical composition. In some embodiments, the steroid and the $CRF_1$ antagonist are administered concurrently in separate pharmaceutical compositions. In some embodiments, the steroid and the $CRF_1$ antagonist are administered sequentially.

## EXAMPLES

**[0136]** The following examples further illustrate the invention but should not be construed as in any way limiting its scope. In particular, the processing conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

**[0137]** All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

**Example 1 – Reduction of DHEAS level in a subject who has polycystic ovary syndrome (PCOS) and elevated adrenal androgens**

**[0138]** Study Compound 3 in a double-blind, proof-of-concept study, evaluating the safety and efficacy of repeated doses of Compound 3 in adults with elevated adrenal androgens, PCOS-FAH or PCOS-FAH+FOH. After screening, eligible subjects with elevated adrenal androgens documented by elevated DHEAS will be randomized to either a compound 3 dose escalation arm or matching placebo arm.

**[0139]** The study is planned as a 3-period study with a duration of 4 weeks for Periods 1 and 2 and a duration of 8 weeks in Period 3 for a total treatment duration of 16 weeks. Subjects randomized to the compound 3 dose escalation arm will be treated with escalating doses of 50-mg, 100-mg or 200 mg based on achieving a DHEAS positive response criteria within each treatment period. Subjects not meeting the criteria will be dose escalated to the next highest dose in the preceding period. Subjects meeting the criteria will remain on their current dose level. Placebo subjects will remain on placebo through the full 16 weeks.

**[0140]** The population are composed of approximately 40 patients, who receive Compound 3 or matching placebo daily for up to 16 weeks. Compound 3 is administered as an oral daily dose. Patients are undergo PK/PD or PD only assessments, approximately every 2 weeks. A follow-up outpatient visit occurs 30 days after the last dose.

**[0141]** Study Design

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 2
- Interventional Study Model: Randomized
- Number of Arms: 2
- Masking: Masking of Study drug
- Allocation: Randomized (1:1)
- Enrollment: 40

**Arms and Interventions:**

| **Arms** | **Assigned Intervention** |
|---|---|
| **Arm 1** | Drug: Compound 3<br>dose escalation (50, 100 and 200-mg) |
| **Arm 2** | Drug: Matching Placebo |

**Outcome Measures**

*Primary Outcome Measures:*

1. Safety and tolerability of Compound 3 in patients with elevated adrenal androgens (adverse effects, serious adverse effects, clinical laboratory parameters, etc.)

[Time Frame: 16 weeks]

*Secondary Outcome Measures:*

2. Proportion of subjects with:
    a. ≥ 30% change from baseline in dehydroepiandrosterone sulfate (DHEAS)
    b. DHEAS <upper limit of normal (ULN)
    c. DHEAS <75$^{th}$ percentile of normal range (Q3)

[Time Fame: 4 to up to 16 weeks]

3. Pharmacokinetics of compound 3

[Time Frame: 4 weeks]

Exploratory Outcome Measure:

4. Changes in PD markers: Changes in cortisol, ACTH, DHEAS, DHEA, A4, T, 17-OHP, 11OHA4, 11OHT, 11KA4, 11KT

[Time Frame: up to 16 weeks]

**Eligibility**

- Minimum Age: 18 Years
- Maximum Age: 30 years
- Sex: Female only
- Gender Based: Yes
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

**Criteria:**

*Inclusion Criteria:*

- Female subjects 18 to 30 years old, inclusive
- Subjects must have documented PCOS according to the NIH (1990) criteria
- BMI ≤38 kg/m$^2$
- DHEAS level > age matched reference ULN at Screening
- Evidence of DHEA hyperresponsiveness to ACTH stimulation during Screening

*Exclusion Criteria:*

- Has a BMI >38kg/m$^2$
- Has PCOS-FOH
- Has HbA1c > 6.5% or Fasting plasma glucose >126 mg/dL
- Has a history that includes bilateral adrenalectomy or hypopituitarism
- Has a history of allergy or hypersensitivity to tildacerfont or any other $CRF_1$ receptor antagonist
- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant uncontrolled psychiatric disorder
- Clinically significant abnormal laboratory finding or assessment
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

**[0142]** While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

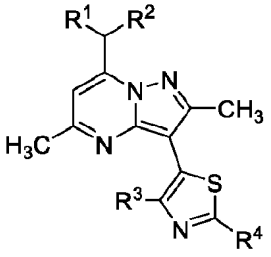
## CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

2. A method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

3. The method of any of claims 1-2, wherein said $CRF_1$ antagonist is a compound of Formula (I):

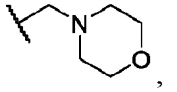
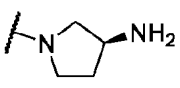
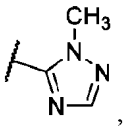
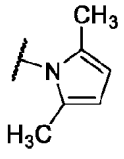


Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ and $R^2$ are independently ethyl or *n*-propyl;

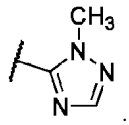
$R^3$ is hydrogen, F, Cl, Br, methyl, trifluoromethyl, or methoxy;

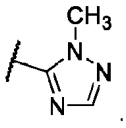
$R^4$ is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ;

$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

4. The method of claim 3, wherein $R^3$ is F, Cl, Br, methyl, or trifluoromethyl.

5. The method of claim 3 or claim 4, wherein $R^3$ is Cl or Br.

6. The method of any one of claims 4 to 5, wherein $R^4$ is $-NR^aR^b$, pyridin-4-yl, morpholin-4-yl, or .

7. The method of any one of claims 4 to 6, wherein $R^4$ is morpholin-4-yl or .

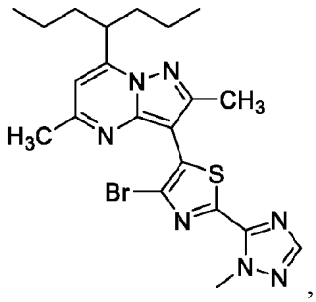
8. The method of any one of claims 4 to 6, wherein $R^4$ is $-NR^aR^b$, and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

9. The method of claim 4, wherein said $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof is 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo[1,5-*a*]pyrimidine.

10. The method of claim 4, wherein said $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

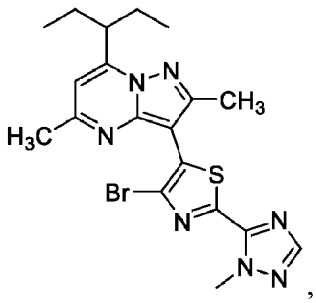
11. The method of claim 4, wherein said $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof is 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

12. The method of claim 4, wherein said $CRF_1$ antagonist is



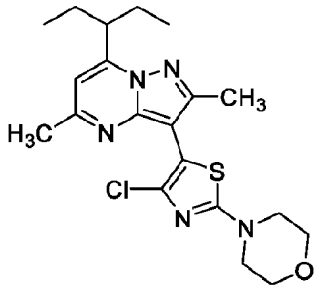
, or a pharmaceutically acceptable salt thereof.

13. The method of claim 4, wherein said $CRF_1$ antagonist is



, or a pharmaceutically acceptable salt thereof.

14. The method of claim 4, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

15. The method of any of claims 1-2, wherein said $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SSR125543 (crinecerfont), and SN003.

16. The method of any one of claims 1-15, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg to about 400 mg total daily dose to the subject.

17. The method of any one of claims 1-15, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 300 mg total daily dose to the subject.

18. The method of any one of claims 1-15, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

19. The method of any one of claims 1-15, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject.

20. The method of any one of claims 1-15, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject.

21. The method of any one of claims 1-15, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 75 mg total daily dose to the subject.

22. The method of any one of claims 1-15, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject.

23. The method of any one of claims 1-15, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject.

24. The method of any one of claims 1-15, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject.

25. The method of any one of claims 1-24, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

26. The method of any one of claims 1-25, wherein an adrenocorticotropic hormone (ACTH) level is reduced by at least 5% from baseline.

27. The method of any one of claims 1-25, wherein an adrenocorticotropic hormone (ACTH) level is reduced by at least 10% from baseline.

28. The method of any one of claims 1-25, wherein a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 5% from baseline.

29. The method of any one of claims 1-25, wherein a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 10% from baseline.

30. The method of any one of claims 1-25, wherein androstenedione (A4) level is reduced by at least 5% from baseline.

31. The method of any one of claims 1-25, wherein androstenedione (A4) level is reduced by at least 10% from baseline.

32. The method of any one of claims 1-25, wherein 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 5% from baseline.

33. The method of any one of claims 1-25, wherein 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 10% from baseline.

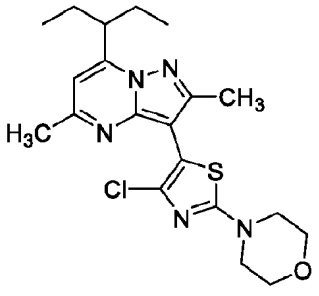
34. The method of any one of claims 1-25, wherein 11β-hydroxytestosterone (11OHT) level is reduced by at least 5% from baseline.

35. The method of any one of claims 1-25, wherein 11β-hydroxytestosterone (11OHT) level is reduced by at least 10% from baseline.

36. The method of any one of claims 25-35, wherein a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 24 hours.

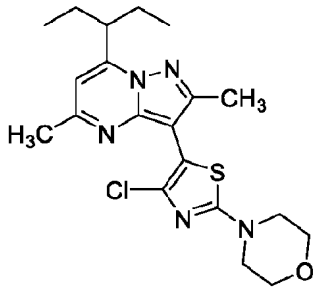
37. The method of any one of claims 25-35, wherein a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 4 weeks.

38. A method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:




; or a pharmaceutically acceptable salt or solvate thereof.

39. A method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH+FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:




; or a pharmaceutically acceptable salt or solvate thereof.

40. The method of either claim 38 or claim 39, wherein Compound 3 is administered at a dose between about 1 mg/day and about 200 mg/day.

41. The method of any of claims 38-40, wherein the pharmaceutical composition comprises between about 1 mg and about 400 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

42. The method of claim 41, wherein the pharmaceutical composition comprises about 25 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

43. The method of claim 41, wherein the pharmaceutical composition comprises about 50 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

44. The method of claim 41, wherein the pharmaceutical composition comprises between about 75 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

45. The method of claim 41, wherein the pharmaceutical composition comprises about 100 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

46. The method of claim 41, wherein the pharmaceutical composition comprises about 200 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

47. The method of claim 41, wherein the pharmaceutical composition comprises about 300 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

48. The method of any one of claims 1-47, wherein the pharmaceutical composition is in the form of microparticles.

49. The method of claim 48, wherein the average size of the microparticles is between about 1 μm to about 20 μm.

50. The method of claim 48, wherein the average size of the microparticles is between about 5 μm to about 15 μm.

51. The method of claim 48, wherein the average size of the microparticles is less than about 10 μm.

52. The method of any of claims 1-47, wherein the pharmaceutical composition is in the form of a capsule or a tablet.

53. The method of claim 52, wherein the capsule is a hard gelatin capsule.

54. The method of claim 52, wherein the capsule is a soft gelatin capsule.

55. The method of any one of claims 52-54, wherein the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

56. The method of any one of claims 52-54, wherein the pharmaceutical composition is free of additional excipients.

57. The method of any one of claims 52-54, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

58. The method of claim 52, wherein the pharmaceutical composition is in the form of a tablet.

59. The method of claim 58, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

60. The method of any one of claims 1-59, wherein the subject is a pediatric patient.

61. The method of any one of claims 1-59, wherein the subject is from about 9 years old to about 18 years old.

62. The method of any one of claims 1-59, wherein the subject is from about 8 years of age to about 55 years of age.

63. The method of any one of claims 1-59, wherein the subject is an adult patient.

64. The method of any of claims 1-63, wherein said subject is treated for a period of about 2 weeks to about 36 weeks.

65. The method of any of claims 1-63, wherein said subject is treated for a period of about 1 month to 12 months.

66. The method of any of claims 1-63, wherein said subject is treated for a period of about 10 months to 50 years.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/45780

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61B 18/14; A61B 18/02; A61B 18/04 (2021.01)

CPC - A61N 1/36117; A61B 18/04; A61B 18/1492

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 2017/0333126 A1 (Medtronic Ardian Luxembourg S.a.r.l.) 23 November 2017 (23.11.2017); abstract | 1-4, 9-15, 38-40 |
| A | US 2010/0222339 A1 (Chen et al.) 02 September 2010 (02.09.2010); abstract, para [0144] | 1-4, 9-15, 38-40 |
| A | US 2018/0110554 A1 (Ziva Medicinal, Inc.) 26 April 2018 (26.04.2018); abstract | 1-4, 9-15, 38-40 |
| A | WO 2019/036472 A1 (SPRUCE BIOSCIENCES, INC.) 21 February 2019 (21.02.2019); entire document | 1-4, 9-15, 38-40 |
| A | US 2013/0045979 A1 (Sanfilippo) 21 February 2013 (21.02.2013); entire document | 1-4, 9-15, 38-40 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 21 November 2021 | DEC 17 2021 |
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Form PCT/ISA/210 (second sheet) (July 2019)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/45780

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-8, 16-37, 41-66
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) **International Patent Classification** 5 :
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Filed on 17 December 1992 (17.12.92)

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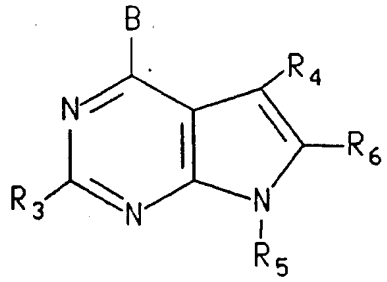
(81) **Designated States:** AU, BR, CA, CZ, JP, KR, NO, NZ, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

**Published**
*With international search report.*

(54) **Title:** PYRROLOPYRIMIDINES AS CRF ANTAGONISTS

(57) **Abstract**

The compounds of formula (I), wherein B, $R_3$, $R_4$, $R_5$ and $R_6$ are as defined herein, are useful in the treatment of stress-related and other diseases. These compounds have corticotropin-releasing factor antagonist activity and as such are of use in the treatment of depression and anxiety related, and other disorders.

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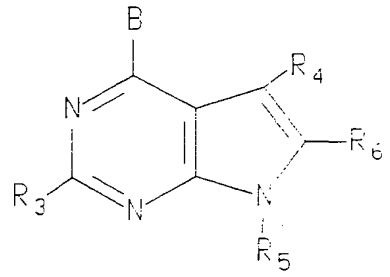
# PYRROLOPYRIMIDINES AS CRF ANTAGONISTS

This invention relates to pyrrolopyrimidines, pharmaceutical compositions containing them, and their use in the treatment of stress-related and other diseases. The compounds have corticotropin-releasing factor (CRF) antagonist activity.

CRF antagonists are mentioned in U.S. Patents 4,605,642 and 5,063,245 referring to peptides and pyrazolinones, respectively. The importance of CRF antagonists is set out in the literature, e.g. as discussed in U.S. Patent 5,063,245, which is incorporated herein by reference. A recent outline of the different activities possessed by CRF antagonists is found in M.J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference. Based on the research described in these two and other references, CRF antagonists are considered effective in the treatment of a wide range of diseases including stress-related illnesses, such as stress-induced depression, anxiety, and headache; abdominal bowel syndrome; irritable colon syndrome; spastic colon; irritable colon; inflammatory diseases; immune suppression; human immunodeficiency virus (HIV) infections; Alzheimer's disease; gastrointestinal diseases; anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction, and fertility problems.

Certain substituted pyrrolopyrimidines have been described in the prior art. U.S. Patent 4,229,453 describes 4-amino substituted pyrrolopyrimidines for treating CNS illnesses or inflammations. Robins, Can. J. Chem., 55, 1251 (1977) describes the antibiotic tubercidin having a 7-ribofuranosyl group attached to 4-aminopyrrolopyrimidine. German Patent Publication 3145287 refers to three 7-bromophenyl-5,6-dimethyl-pyrrolopyrimidines as having analgesic, sedative, anti-convulsant and anti-inflammatory activity.

The present invention relates to a compound of the formula




I

and the pharmaceutically acceptable acid addition salts thereof, wherein

B is $NR_1R_2$, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$;

$R_1$ is hydrogen, or $C_1$-$C_6$ alkyl which may be substituted by one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $C_1$-$C_8$ alkoxy, O-C -($C_1$-$C_6$ alkyl), O-C NH($C_1$-$C_4$ alkyl), O-C -N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), amino, NH($C_1$-$C_4$ alkyl), N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), S($C_1$-$C_6$ alkyl), N($C_1$-$C_4$ alkyl)C ($C_1$-$C_4$ alkyl), NHC ($C_1$-$C_4$ alkyl), COOH, C O($C_1$-$C_4$ alkyl), C NH($C_1$-$C_4$ alkyl), C N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), SH, CN, $NO_2$, SO($C_1$-$C_4$ alkyl), $SO_2$($C_1$-$C_4$ alkyl), $SO_2NH$($C_1$-$C_4$ alkyl), $SO_2N$($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), and said $C_1$-$C_6$ alkyl may contain one or two double or triple bonds;

$R_2$ is $C_1$-$C_{12}$ alkyl, aryl or ($C_1$-$C_{10}$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or ($C_1$-$C_6$ alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, benzyl or $C_1$-$C_4$ alkanoyl, wherein $R_2$ may be substituted independently by from one to three of chloro, fluoro, or $C_1$-$C_4$ alkyl, or one of hydroxy, bromo, iodo, $C_1$-$C_6$ alkoxy, O-C -($C_1$-$C_6$ alkyl), O-C -N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), S($C_1$-$C_6$ alkyl), $NH_2$, NH($C_1$-$C_2$ alkyl), N($C_1$-$C_2$ alkyl) ($C_1$-$C_4$ alkyl), N($C_1$-$C_4$ alkyl)-C ($C_1$-$C_4$ alkyl), NHC ($C_1$-$C_4$ alkyl), COOH, C O($C_1$-$C_4$ alkyl), C NH($C_1$-$C_4$ alkyl), C N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), SH, CN, $NO_2$, SO($C_1$-$C_4$ alkyl), $SO_2$($C_1$-$C_4$ alkyl), $SO_2NH$($C_1$-$C_4$ alkyl), $SO_2N$($C_1$-$C_4$ alkyl)($C_1$-

$C_2$ alkyl), and wherein said $C_1$-$C_{12}$ alkyl or $C_1$-$C_{10}$ alkylene may contain one to three double or triple bonds; or

$NR_1R_2$ or $CR_1R_2R_{11}$ then $R_1$ and $R_2$ taken together with the atom to which they are attached may form a saturated 3- to 8-membered ring of which the 5- to 8-membered ring may contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl or benzyl;

$R_3$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, $O(C_1$-$C_6$ alkyl), $NH(C_1$-$C_6$ alkyl), $N(C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), SH, $S(C_1$-$C_4$ alkyl), $SO(C_1$-$C_4$ alkyl), or $SO_2(C_1$-$C_4$ alkyl), wherein said $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl may contain one double or triple bond and may be substituted by from 1 to 3 substituents $R_8$ independently selected from the group consisting of hydroxy, $C_1$-$C_3$ alkoxy, fluoro, chloro or $C_1$-$C_3$ thioalkyl;

$R_4$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, formyl, $NH(C_1$-$C_6$ alkyl), $N(C_1$-$C_6$ alkyl)($C_1$-$C_2$ alkyl), $SO_n(C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said $C_1$-$C_6$ alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, $NHC(=O)(C_1$-$C_4$ alkyl), $NH(C_1$-$C_4$ alkyl), $N(C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), $C(=O)O(C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

$R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl or benzyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, $NH(C_1$-$C_4$ alkyl), $N(C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), $COO(C_1$-$C_4$ alkyl), $CO(C_1$-$C_4$ alkyl), $SO_2NH(C_1$-$C_4$ alkyl), $SO_2N(C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), $SO_2NH_2$, $NHSO_2(C_1$-$C_4$ alkyl), $S(C_1$-$C_6$ alkyl), $SO_2(C_1$-$C_6$ alkyl), wherein said $C_1$-$C_4$ alkyl

and $C_1$-$C_6$ alkyl may be substituted by one or two of fluoro, chloro, hydroxy, $C_1$-$C_4$ alkoxy, amino, methylamino, dimethylamino or acetyl wherein said $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl may contain one double or triple bond; with the proviso that $R_5$ is not unsubstituted phenyl;

$R_6$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, formyl, amino, $NH(C_1$-$C_6$ alkyl), $N(C_1$-$C_6$ alkyl)($C_1$-$C_2$ alkyl), $SO_n(C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said $C_1$-$C_6$ alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, NHC($C_1$-$C_4$ alkyl), $NH(C_1$-$C_4$ alkyl), $N(C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), C O($C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

$R_{11}$ is hydrogen, hydroxy, fluoro, chloro, COO($C_1$-$C_2$ alkyl), cyano, or CO($C_1$-$C_2$ alkyl); and

$R_{12}$ is hydrogen or $C_1$-$C_4$ alkyl; with the proviso that (1) B is not straight chain alkyl, (2) when $R_5$ is unsubstituted cycloalkyl, $R_3$ and $R_4$ are hydrogen, and $R_6$ is hydrogen or methyl, then B is not $NHR_2$ wherein $R_2$ is benzyl or thienylmethyl, and (3) when $R_5$ is p-bromophenyl, and $R_3$, $R_4$ and $R_6$ are methyl, then B is not methylamino or hydroxyethylamino.

Preferred compounds of the formula I of the invention are those wherein B is $NR_1R_2$, $NHCHR_1R_2$, or $OCHR_1R_2$, wherein $R_1$ is $C_1$-$C_6$ alkyl, which may be substituted by one of hydroxy, fluoro or $C_1$-$C_2$ alkoxy, and may contain one double or triple bond; those wherein $R_2$ is benzyl or $C_1$-$C_6$ alkyl which may contain one double or triple bond, wherein said $C_1$-$C_6$ alkyl or the phenyl in said benzyl may be substituted by fluoro, $C_1$-$C_6$ alkyl, or $C_1$-$C_6$ alkoxy; those wherein $R_3$ is methyl, ethyl, fluoro, chloro or methoxy; those wherein $R_4$ and $R_6$ are independently hydrogen, methyl, or ethyl; and those wherein $R_5$ is phenyl substituted by two or three substituents, said substituent being independently fluoro, chloro, bromo, iodo, $C_1$-$C_4$ alkoxy, trifluoromethyl, $C_1$-$C_6$ alkyl which may be substituted by one of hydroxy, $C_1$-$C_4$ alkoxy or fluoro and may have one double or triple bond, -($C_1$-$C_2$ alkylene)O($C_1$-$C_2$ alkyl), $C_1$-$C_3$ hydroxyalkyl, hydroxy, formyl, COO($C_1$-$C_2$ alkyl), -($C_1$-$C_2$ alkylene)amino, or -C(O)($C_1$-$C_2$ alkyl).

Specific preferred compounds include:

n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;

4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;

n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine;

2-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;

2-(S)-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;

4-(1-ethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;

4-(1-methoxymethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;

4-(1-ethyl-butyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo-[2,3-d]pyrimidine;

[7-(4-bromo-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-(1-methoxymethyl-propyl)-amine;

2-[7-(2-bromo-4,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;

2-[7-(4-ethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;

2-[7-(2-ethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol; and

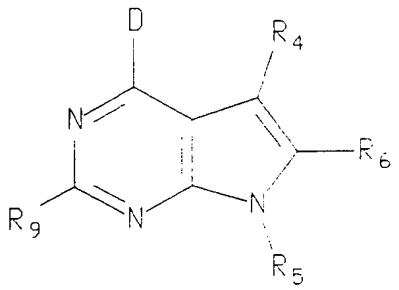
2-[7-(2-fluoromethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol.

The invention also relates to a pharmaceutical composition for the treatment of illnesses induced or facilitated by corticotropin releasing factor which comprises a compound of the formula I as defined above in an amount effective in the treatment of said illnesses, and a pharmaceutically acceptable carrier, and a pharmaceutical composition for the treatment of inflammatory disorders, such as arthritis, asthma and allergies; anxiety; depression; fatigue syndrome; headache; pain; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; and fertility problems, which comprises a compound of the formula I as defined above in an amount effective in the treatment of said disorders, and a pharmaceutically acceptable carrier. Preferred compositions of the invention are those containing preferred compounds of formula I as described above.

The invention further relates to a method for the treatment of illnesses induced or facilitated by corticotropin releasing factor by administering to a subject in need of such treatment a compound of formula I as defined above in an amount effective in such treatment, and a method for the treatment of inflammatory disorders, such as arthritis, asthma and allergies; anxiety; depression; fatigue syndrome; headache; pain; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; and fertility problems, particularly depression and anxiety, by administering to a subject in need of such treatment a compound of formula I as defined above in an amount effective in

such treatment. Preferred methods of the invention are those administering a preferred compound of the formula I as described above.

The invention also relates to an intermediate compound of the formula



I

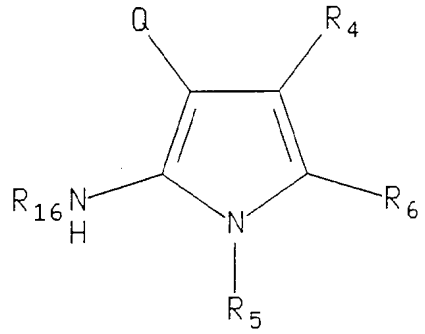
wherein

D is hydroxy, chloro, or cyano,

$R_4$ and $R_6$ are each independently hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, $SO_n(C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, or cyano, wherein said $C_1$-$C_6$ alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, $NH\overset{O}{\overset{\|}{C}}(C_1$-$C_4$ alkyl), $NH(C_1$-$C_4$ alkyl), $N(C_1$-$C_4$ alkyl)$(C_1$-$C_2$ alkyl), $\overset{O}{\overset{\|}{C}}O(C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

$R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperdinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl or phenylmethyl, wherein each of the above groups may be substituted independently by from one to three of fluoro, chloro, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy or trifluoromethyl, or one of bromo, iodo, cyano, nitro, amino, $NH(C_1$-$C_4$ alkyl), $N(C_1$-$C_4)(C_1$-$C_2$ alkyl), $COO(C_1$-$C_4$ alkyl), $CO(C_1$-$C_4$ alkyl), $SO_2NH(C_1$-$C_4$ alkyl), $SO_2N(C_1$-$C_4$ alkyl)$(C_1$-$C_2$ alkyl), $SO_2NH_2$, $NHSO_2(C_1$-$C_4)$, $S(C_1$-$C_6$ alkyl), $SO_2(C_1$-$C_6$ alkyl), wherein said $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that $R_5$ is not unsubstituted phenyl; and

$R_9$ is hydrogen, $C_1$-$C_6$ alkyl or chloro; with the proviso that when (a) $R_4$ and $R_6$ are methyl, $R_9$ is hydrogen and D is hydroxy, then $R_5$ is not phenyl (1) substituted by one of halogen, nitro, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, or trifluoromethyl, and optionally in addition substituted by one or two of halogen, $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkoxy, or (2) di-or trisubstituted by one of nitro or trifluoromethyl and one or two of halogen, $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkoxy, and (b) when D is chloro, $R_4$ and $R_9$ are hydrogen, and $R_6$ is $C_1$-$C_6$ alkyl, then $R_5$ is not unsubstituted cyclohexyl; and a compound of the formula



VII

wherein

Q is $C(O)CHR_1R_2$ or cyano;

$R_1$ is hydrogen, or $C_1$-$C_6$ alkyl which may be substituted by one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $C_1$-$C_8$ alkoxy, $S(C_1$-$C_6$ alkyl), or nitro, and said $C_1$-$C_6$ alkyl may contain one or two double or triple bonds;

$R_2$ is $C_1$-$C_{12}$ alkyl, aryl or ($C_1$-$C_{10}$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or ($C_1$-$C_6$ alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, benzyl or $C_1$-$C_4$ alkanoyl, wherein $R_2$ may be substituted independently by from one to three of chloro, fluoro, or $C_1$-$C_4$ alkyl, or one of hydroxy, bromo, iodo, $C_1$-$C_6$ alkoxy, $S(C_1$-$C_6$ alkyl), or nitro, and wherein said $C_1$-$C_{12}$ alkyl or $C_1$-$C_{10}$ alkylene may contain one to three double or triple bonds; or

$R_4$ and $R_6$ are each independently hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, amino, $SO_n(C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, cyano, wherein said

$C_1$-$C_6$ alkyl may be substituted by one $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

$R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy or trifluoromethyl, or one of bromo, iodo, cyano, nitro, amino. $NH(C_1$-$C_4$ alkyl), $N(C_1$-$C_4)(C_1$-$C_2$ alkyl), $COO(C_1$-$C_4$ alkyl), $CO(C_1$-$C_4$ alkyl), $SO_2NH(C_1$-$C_4$ alkyl), $SO_2N(C_1$-$C_4$ alkyl)$(C_1$-$C_2$ alkyl), $SO_2NH_2$, $NHSO_2(C_1$-$C_4$ alkyl), $S(C_1$-$C_6$ alkyl), $SO_2(C_1$-$C_6$ alkyl), wherein said $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that $R_5$ is not unsubstituted phenyl; and $R_{16}$ is hydrogen or $C(O)C_1$-$C_6$ alkyl; with the proviso that when Q is cyano, $R_4$ and $R_6$ are not both methyl.

Whenever reference is made to alkyl, this includes both straight and branched chain alkyl.

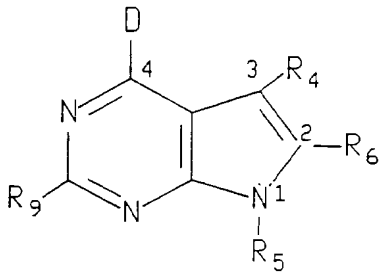
Whenever reference is made herein to 3-to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl containing one to three of O, S or N-Z, it is understood that the oxygen and sulfur ring atoms are not adjacent to each other. The three membered cycloalkyl has just one O, S or N-Z. An example of a six-membered cycloalkyl having O and N is morpholinyl.

Whenever $R_2$ or $R_5$ is a heterocyclic group, the attachment of the group is through a carbon atom.

Whenever reference is made herein to $C_1$-$C_4$ alkyl or $C_1$-$C_6$ alkyl which "may contain one or two double or triple bonds" in the definitions of $R_1$, $R_2$ and $R_3$, it is understood that at least two carbons are present in the alkyl for one double or triple bond, and at least four carbons for two double and triple bonds.

Whenever an alkoxy group, e.g. in the definitions of $R_1$ and $R_2$, may have a double or triple bond, it is understood that such double or triple bond is not directly attached to the oxygen.

The compounds of formula I wherein B is $NR_1R_2$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, or $NHNR_1R_2$, and $R_3$ is hydrogen, $C_1$-$C_6$ alkyl or chloro (hereafter $R_9$) may be prepared by reaction of a compound of the formula



II

wherein D is Cl, and $R_4$, $R_5$ and $R_6$ are as defined above with reference to formula I, with a compound of the formula BH wherein B is as defined immediately above. The reaction is carried out in a solvent in the presence of a base at a temperature of between about 0° to about 150°C. Suitable solvents are organic solvents such as acetonitrile, dimethylsulfoxide, acetone, $C_2$-$C_{15}$ alkyl alcohol, tetrahydrofuran, chloroform, benzene, xylene or toluene, preferably acetontrile or dimethylsulfoxide.

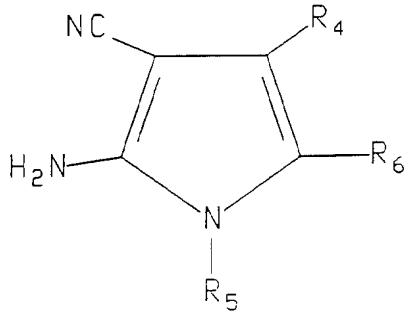
When B is $NR_1R_2$, $NHNR_1R_2$, or $NHCR_1R_2R_{11}$, an excess of BH is used. Other bases such as potassium carbonate or tri-($C_1$-$C_6$)alkyl amine may be used instead. The reaction is carried out at a temperature of about 75° to 150°C. When the reaction is carried out in the presence of a base, such as sodium hydride or potassium $C_1$-$C_4$ alkoxide, a molar equivalent of the amine is used. When B is $OCR_1R_2R_{11}$ or $SCR_1R_2R_{11}$, a base which is capable of deprotonation of BH may be used, such as an alkali metal hydride such as sodium or potassium hydride, or an organometallic base such as sodium diisopropylamide, sodium bis(trimethylsily)amide, lithium diisopropylamide, lithium bis(trimethylsily)amide, sodium $C_1$-$C_4$ alkoxide or n-butylithium. The solvent used is dry tetrahydrofuran, dimethylsulfoxide, methylene chloride, or toluene, and the reaction temperature is between about -78°C and the reflux temperature of the reaction mixture, preferably 0°C to 80°C.

The compounds of formula I wherein $R_3$ is the groups other than $R_9$ (hereafter $R_{10}$) may be prepared by reacting a compound of the formula I wherein $R_3$ is chloro with a nucleophile of the formula $R_{10}H$ with or without an organic or inorganic base. Suitable bases include sodium, sodium hydride, and alkali metal hydroxide such as potassium hydroxide, and weaker bases such as potassium carbonate or triethylamine.

The latter are generally used when $R_{10}H$ is alkanol, $C_1$-$C_6$ alkanethiol, an amine, e.g. $NH(C_1$-$C_6$ alkyl), or tetrahydrobutyl ammonium fluoride. Suitable solvents are dimethylsulfoxide, acetonitrile, $C_1$-$C_5$ alkyl alcohol, tetrahydrofuran, benzene, toluene or methylene chloride.

The compounds of formula II wherein D is chloro may be prepared by reacting the corresponding 4-hydroxy compound of formula III (not shown) with an excess of phosphorus oxychloride or thionyl chloride at temperatures between about 60 to 140°C, conveniently at the reflux temperature of the reaction mixture. When the reaction is carried out in a solvent, suitable solvents are halogenated alkanes, such as methylene chloride or chloroform. The reaction may be in the presence of a base such as N,N-diethylaniline, trimethylamine or potassium carbonate.

The compounds of formula III wherein $R_9$ is hydrogen may be prepared by reaction of a compound of the formula




IV

wherein $R_4$, $R_5$, and $R_6$ are as defined with reference to formula I with formic acid at a temperature between about 60 to 140°C, preferably at the reflux temperature of the reaction mixture.

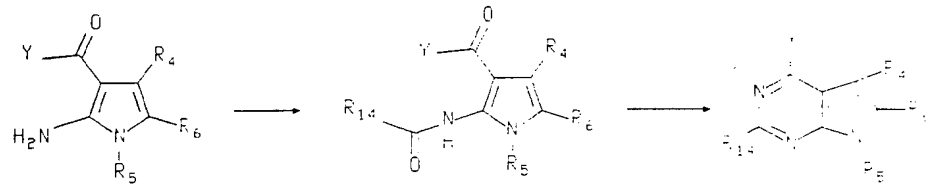
The compounds of formula III wherein $R_9$ is $C_1$-$C_6$ alkyl (hereafter $R_{13}$) may be prepared by reacting a compound of formula IV with $R_{13}COOCOR_{13}$ in $R_{13}COOH$ or $R_{13}CO(OC_1$-$C_2$ alkyl)$_3$ in acetic acid or an appropriate organic solvent such as ethyl acetate or toluene, at a temperature between 25° to 120°C, preferably at the reflux temperature of the reaction mixture. The compounds of formula III wherein $R_9$ is hydroxy may be prepared by reacting a compound of formula IV with chlorosulfonyl isocyanate in an appropriate solvent at temperature between -78°C to 100°C, preferably at -20°C to 60°C, followed by acid hydrolysis. The appropriate solvents include methylene chloride, dimethyl formamide, tetrahydrofuran, and toluene.

preferably dimethyl formamide or methylene chloride. The above formed compounds wherein $R_9$ is hydrogen, $C_1$-$C_6$ alkyl or hydroxy may be heated in aqueous acid to give the compounds of formula III. The appropriate aqueous acids are 85% phosphoric acid, hydrochloric acid, sulfuric acid, or acetic acid, preferably 85% phosphoric acid. The reaction is generally carried out at about 25 to 150°C, preferably 80 to 130°C. Alternatively, the formed compounds may be heated with phosphorous pentoxide and N,N-dimethylcyclohexanamine at about 150 to 200°C.

The compounds of formula IV may be prepared by conventional methods.

The compounds of formula I wherein B is $CR_1R_2R_{11}$ and $R_3$ is hydrogen, $C_1$-$C_6$ alkyl, or hydroxy (hereafter $R_{14}$) may be prepared, as depicted in Scheme 1, by heating a compound of the formula VI, wherein $R_{14}$ is hydrogen, $C_1$-$C_6$ alkyl or amino, $R_1$, $R_2$, $R_{11}$, $R_4$, $R_5$, and $R_6$ are as defined above, and Y is $CR_1R_2R_{11}$, with ammonium chloride and $R_{14}CONH_2$ at reflux temperatures.

Scheme 1



V VI I-A

The compounds of formula I wherein B is $CR_1R_2R_{11}$ as defined above with reference to formula I and $R_3$ is as defined above with reference to formula I, other than hydrogen, $C_1$-$C_6$ alkyl, or hydroxy, may be prepared by reacting the 2-chloro derivatives of formula I wherein $R_3$ is chloro (formula I-B, not shown) with a nucleophile of formula $R_{15}H$ with or without an organic or inorganic base by the method described previously for the reaction with $R_{10}H$, wherein $R_{15}$ is $R_3$ other than hydrogen, $C_1$-$C_6$ alkyl, hydroxy, and chloro. The compounds of formula I-B may be prepared by a method analogous to that for the conversion of compounds III to compounds II wherein D is chloro.

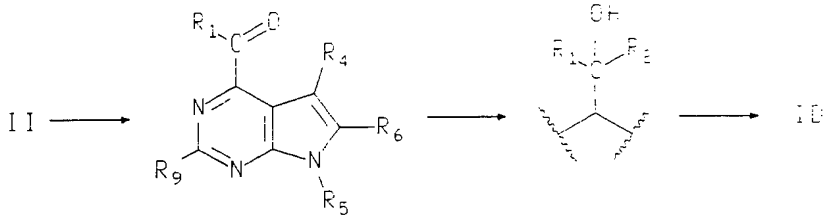
The compounds of formula VI may be prepared, as shown in Scheme I, starting from compounds of the formula V by methods analogous to those for the conversion of compounds IV to compounds III.

The compounds of formula V may be prepared by methods analogous to the conventional methods used for the preparation of compounds of formula IV by using $YCOCH_2CN$ instead of malonitrile, wherein Y is $CR_1R_2R_{11}$.

The compounds of formula I wherein B is $C(O)R_2$ may be prepared by reacting a compound of formula II wherein D is cyano with a Grignard reagent containing group $R_2$, e.g. $R_2MgCl$, or $R_2MgBr$.

The compounds of formula I wherein B is $CR_1R_2R_{11}$, $C(C=CR_2R_{12})R_1$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$ or $C(O)R_2$, and $R_3$ is $R_9$ as defined above with reference to formula II, may be prepared as depicted in Scheme 2.

Scheme 2




The compounds of formula II wherein D is cyano and $R_4$, $R_5$, $R_6$ and $R_9$ are as defined above, prepared by reacting the corresponding compound wherein D is chloro with potassium cyanide in dimethylsulfoxide, are reacted with a Grignard reagent containing group $R_1$ as defined above to form the compound of formula VII. Further reaction of the compound of formula VII with a Grignard reagent containing group $R_2$ as defined above provides the compound of formula IC. Corresponding compounds of formula ID wherein B is $CR_1R_2R_{11}$ or $C(=CR_1R_{12})R_1$ may be prepared by conventional methods. Thus, reaction of IC with an acid, such as concentrated sulfuric acid or hydrochloric acid, gives a compound of formula I wherein B is $C(=CR_2R_{12})R_1$. Hydrogenation of a compound wherein B is $C(=CR_2R_{12})R_1$ using Pd/C or platinum oxide catalyst gives a compound I wherein B is $CHR_1R_2$. Reaction of a compound I wherein B is $CR_1R_2OH$ with diethylamino sulfur trifluoride or triphenylphosphine carbontetrachloride affords a compound I wherein B is $CR_1R_2F$ or $CR_1R_2Cl$, respectively.

When the compounds of the invention contain one or more chiral centers, it is understood that the invention includes the racemic mixture and the individual diastereomers and enantiomers of such compounds.

The acid addition salts of the compounds of formula I are prepared in a conventional manner by treating a solution or suspension of the free base of formula I with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques are employed in isolating the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, mandelic, di-p-toluoyl-L-tartaric and related acids.

The novel compound of the invention of formula I may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple, e.g. up to three, doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of formula I and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions of the novel compound of formula I in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular

aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Additionally, it is possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes and ointments in accordance with standard pharmaceutical practice.

The effective dosage for the compound of formula I depends on the intended route of administration and other factors such as age and weight of the patient, as generally known to a physician. The dosage also depends on the illness to be treated. The daily dosage will generally range from about 0.1 to 50 mg/kg of the body weight of the patient to be treated. For treatment of inflammatory diseases about 0.1 to about 100 mg/kg will be needed, for Alzheimer's disease, about 0.1 to about 50 mg/kg, as well as for gastrointestinal diseases, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, etc.

The methods for testing the compounds for formula I for their CRF antagonist activity are according to the procedures of Endocrinology, 116, 1653-1659 (1985) and Peptides, 10, 179-188 (1985) which determine the binding affinity of a test compound for a CRF receptor. The binding affinities for the compounds of formula I. expressed as $IC_{50}$ values, generally range from about 0.2 nanomolar to about 10 micromolar.

The following Examples illustrate the invention. The following abbreviations are used: Ph=phenyl, Me=methyl, Bu=butyl, Et=ethyl, Pr=propyl.

Example 1

A. 2-amino-4-methyl-1-(2,4,6-trimethylphenyl)pyrrole-3-carbonitrile

A mixture 2-(2-bromo-1-methyl-ethylidene)-malononitrile and 2,4,6-trimethylaniline (17.330 g, 91.24 mmol) in 40 mL of isopropanol was stirred at room temperature for 15 hours. The reaction mixture was concentrated to dryness and diluted with chloroform and water. The chloroform layer was neutralized with dilute sodium hydroxide and washed with brine, separated, dried and concentrated to give 33.000 g of brown oily solid. The solid was purified through silica gel column chromatography to give 9.35 g (47.5%) of the title compound as an orange-yellow solid. $^1H$ NMR ($CDCl_3$) $\delta$ 2.0(s.6H). 2.15(s,3H), 2.35(s,3H), 3.75(brs.2H). 5.8(s.1H), 6.95(s,2H) ppm.

B. N-[3-cyano-4-methyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-2-yl]-acetamide

A mixture of the purified compound of step A (3.000 g, 12.54 mmol) and acetic anhydride (1.410 g, 1.31 ml, 13.82 mmol) in 3 ml of acetic acid was refluxed for 45 minutes, cooled and poured onto crushed ice and extracted with ethyl acetate. The organic layer was neutralized, dried and concentrated to give 3.71 g (105%) of dark-pink glass foam. $^1$H NMR ($CDCl_3$) $\delta$ 1.95(s,6H), 2.2(s,3H), 2.32 (s,3H), 6.2(s,1H), 6.8(brs, 1H, NH), 6.9(s,2H) ppm.

C. 2,5-dimethyl-7-(2,4,6-trimethylphenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one

A suspension of the compound of step B (3.200 g, 11.38 mmol) in 3 ml of 85% phosphoric acid was immersed in an oil bath preheated to 130°C for 30 minutes. The reaction mixtures was cooled and poured onto crushed ice and stirred until solid formed and ice melted. The solid was filtered, washed with water to give a tannished solid, the title compound, which was purified through silica gel column chromatography to give a tan solid. $^1$H NMR ($CDCl_3$) $\delta$ 1.92(s,6H), 2.32(s,3H), 2.41(s,3H), 2.45(s,3H), 2.46(s,3H), 6.42(d,1H), 6.95(s,2H) ppm.

D. 4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo-[2,3-d]pyrimidine

A mixture of the compound of step C (1.030 g, 3.67 mmol) and $POCl_3$ (3 ml) was heated at reflux for 2.5 hours and cooled. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with dilute sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated to dryness to give the title compound as a tan solid which was purified through silica gel to give an off-white solid. $^1$H NMR ($CDCl_3$) $\delta$ 1.90(s,6H), 2.35(s,3H), 2.50(s,3H), 2.65(s,3H), 6.78(s,1H), 7.00(s,2H) ppm.

EXAMPLE 2

A. 2-amino-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrole-3-carbonitrile

A mixture of 3-hydroxy-2-butanone (100.000 g, 1.135 mol), 2,4,6-trimethylaniline (153.225 g, 1.135 mol) and p-toluenesulfonic acid (0.670 g) in 500 ml of benzene was refluxed using a Dean-Stark trap to remove water. After 2 hours,malononitrile (75.000 g, 1.135 mol) was added and the mixture was refluxed for an additional 10 hours until all the staring material was consumed. The reaction mixture was cooled and precipitate formed and filtered. The solid was washed with a minimum amount of ethanol. The

solid was diluted with 500 ml of benzene and product was dissolved. Some undesired product was insoluble and was filtered off. The filtrate was concentrated to give a tan solid which was recrystallized from ethanol to give 130.260 g of off-white crystals. $^1$H NMR ($CDCl_3$) $\delta$ 1.68(s,3H), 1.93(s,6H), 2.05(s,3H), 2.31(s,3H), 3.62(brs,2H), 6.95(s,2H) ppm.

B. N-[3-cyano-4,5-dimethyl-1-(2,4,6-trimethyphenyl)-1H-pyrrol-2-yl]-acetamide

The title compound was prepared as a tan solid by the procedure analogous to that of Example 1A starting with the compound of step A and acetic anahydride in acetic acid. The crude material was pure and used directly for the next cyclization step. $^1$H NMR ($CDCl_3$) $\delta$ 1.75(s,3H), 1.80(s,6H), 1.95(s,3H), 2.18(s,3H), 2.30(s,3H), 6.60(brs, 1H), 6.93(s,2H) ppm.

C. 2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-3,7-dihydro-pyrrol[2,3-d]pyrimidin-4-one

A mixture of the compound of step B(157.600 g, 0.53 mol) and 100 ml of 85% phosphoric acid was heated for 0.5 hours in an oil bath at a temperature of 130°C. All the starting material was consumed and the desired product formed. The mixture was cooled, poured into 1200 ml of ice-water, and stirred. Precipitate formed and was filtered. The solid was washed with water, dried overnight to give 113.220 g of the title compound as brick-pink solid. $^1$H NMR ($CDCl_3$) $\delta$ 1.85(s,6H), 1.87(s,3H), 2.34(s,3H), 2,41(s,3H), 2.44(s,3H), 7.00(s,2H) ppm.

EXAMPLE 3

A. 2-amino-4,5-diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrole-3-carbonitrile

The crude material of the title compound was prepared as an oil by the procedure analogous to that of Example 2A starting with 4-hydroxy-3-hexanone. The crude material was used directly for the next acetylation step without further purification.

B. N-[3-cyano-4,5-diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-2-yl]-acetamide

The title compound was prepared as an oil by the procedure of Example 1A starting with the compound of above step A and acetic anhydride in acetic acid. The crude material was purified through silica gel column chromatography using chloroform as eluent to give the title compound as an oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.85(t,3H), 1.26(t,3H), 1.92(s,6H), 2.19(s,3H), 2.23(q,2H), 2.33(s,3H), 2.59(q,2H), 6.95(s,2H) ppm.

C. 2-methyl-5,6-diethyl-7-(2,4,6-trimethylphenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one

The title compound was prepared as a brown solid by the procedure of Example 2C starting with the compound of above step B and 85% phosphoric acid. The crude material was used directly for the next chlorination reaction without further purification.

EXAMPLE 4

The following compounds were prepared according to the method of Example 1 starting from the corresponding 2,5,6-trialkyl-7-(2,4,6-trimethylphenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one.

4-chloro-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine - a tan solid. $^1$H NMR ($CDCl_3$) $\delta$ 1.81(s,6H), 1.99(s,3H), 2.35(s,3H), 2.46(s,3H), 2.59(s,3H), 7.01(s,2H) ppm.

4-chloro-2-methyl-5,6-diethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin - a tan solid. $^1$H NMR ($CDCl_3$) $\delta$ 0.96(t,3H), 1.31(t,3H), 1.85(s,6H), 2.38(s,3H), 2.46(q,2H), 2.62(s,3H), 2.62(s,2H), 2.92(q,2H), 7.02(s,2H) ppm.

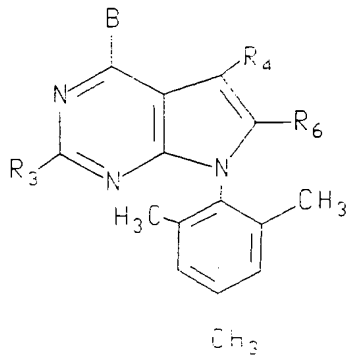
EXAMPLE 5

Butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine

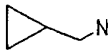
A mixture of 4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine (1.000 g, 3.36 mmol) and N-ethylbutylamine (3.400 g, 33.60 mmol) in 5 ml of dimethylsulfoxide was heated to reflux for 1.5 hours. The mixture was cooled and treated with water and a few drops of 2 N HCl to pH 6.5 and extracted with ethyl acetate. The organic layer was separated, washed with dilute sodium bicarbonate, brine, and dried over sodium sulfate anhydrous and concentrated to dryness. The residue was purified through silica gel column chromatography to give 995 mg (81% yield) of the title compound as an oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.90 (t,3H), 1.23(t,3H), 1.35(m,2H), 1.60-1.70(m,2H), 1.92(s,6H), 2.30(s,3H), 2.40(s,3H), 2.46(s,3H), 3.58(t,2H), 3.66(q,2H), 6.55(s,1H), 6.95(s,2H) ppm. The corresponding hydrogen chloride salt was prepared as a white crystals after recrystallization from ethyl acetate. $^1$H NMR ($D_2O$) $\delta$ 0.90(t,3H), 1.34(m,5H), 1.75(m,2H), 1.90(s,6H), 2.37(s,3H), 2.48(s,3H), 2.55(s,3H), 3.80-3.94(m,4H), 7.09(s,2H) ppm.

EXAMPLE 6

The following compounds were prepared starting with the appropriate amine and the appropriate 4-chloro-2,5,6-trialkyl-7-(substituted phenyl)-7H-pyrrolo[2,3-d]pyrimidine and employing the general procedure of Example 5.



| B | $R_3$ | $R_4$ | $R_6$ | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|---|
| $NMe_2$ | Me | Me | Me | 1.82(s,6H), 2.00(s,3H) 2.38(s,3H) 2.40(s,3H), 2.90(s,3H), 3.58(s,6H), 7.03(s,2H) |
| $NEt_2$ | Me | Me | Me | 1.22(t,6H), 1.84(s,6H), 1.94(s,3H), 2.35(s,3H), 2.38(s,3H), 2.55(s,3H), 3.60(q,4H), 6.98(s,2H) |
| $N(n\text{-}Pr)_2$ | Me | Me | Me | 0.90(t,6H), 1.68(q,4H), 1.85(s,6H), 1.95(s,3H), 2.35(s,3H), 2.39(s,3H), 2.48(s,3H), 3.53(q,4H), 6.99(s,2H) |
| $N\text{-}(n\text{-}Bu)_2$ | Me | Me | Me | 0.88(t,6H), 1.30(m,4H), 1.61(m,4H), 1.82(s,6H), 1.92(s,3H), 2.30(s,3H), 2.34(s,3H), 2.47(s,3H), 3.50(t,4H), 6.95(s,2H) |
| EtN(n-Pr) | Me | Me | Me | 0.92(t,3H), 1.20(t,3H), 1.64(m,2H), 1.85(s,6H), 1.94(s,3H), 2.35(s,3H), 2.38(s,3H), 2.47(s,3H), 3.49(t,2H), 3.59(q,2H), 6.99(s,2H) |
| EtN(n-Bu) | Me | Me | Me | 0.90(t,3H), 1.19(t,3H), 1.33(m,2H), 1.60(m,2H), 1.83(s,6H), 1.92(s,3H), 2.33(s,3H), 2.35(s,3H), 2.45(s,3H), 3.51(t,2H), 3.58(q,2H), 6.96(s,2H) |

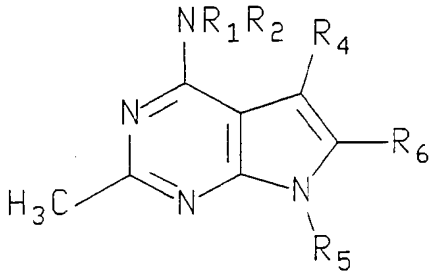
| B | $R_3$ | $R_4$ | $R_6$ | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|---|
| $EtN(CH_2)_2OH$ | Me | Me | Me | 1.25(t,3H), 1.78(s,6H), 1.90(s,3H), 2.30(s,3H), 2.36(s,3H), 2.40(s,3H), 3.64(q,2H), 3.75(m,2H), 3.86(t,2H), 6.96(s,2H) |
| $(n\text{-}Bu)N(CH_2)_2OH$ | Me | Me | Me | 0.95(t,3H), 1.35(m,2H), 1.71(m,2H), 1.81(s,6H), 1.92(s,3H), 2.31(s,3H), 2.37(s,3H), 2.44(s,3H), 3.55(dd,2H), 3.72(t,2H), 3.87(t,2H), 6.95(s,2H) |
| $MeN(CH_2CHMe_2)$ | Me | Me | Me | 0.89(s,3H), 0.91(s,3H), 1.81(s,6H), 1.91(s,3H), 1.96-2.10(m,1H), 2.32(s,3H), 2.35(s,3H), 2.43(s,3H), 3.11(s,3H), 3.32(d,2H), 6.95(s,2H) |
|  | Me | Me | Me | 0.35(dd,2H), 0.47(m,2H), 0.90(t,3H), 1.10(m,1H), 1.67(m,2H), 1.83(s,6H), 1.93(s,3H), 2.33(s,3H), 2.37(s,3H), 2.45(s,3H), 3.41(d,2H), 3.62(t,2H), 6.97(s,2H) |
| $N(CH_2CH{=}CH)_2$ | Me | Me | Me | 1.85(s,6H), 1.96(s,3H), 2.36(s,3H), 2.39(s,3H), 2.49(s,3H), 4.18(d,4H), 5.20-5.32(m,4H), 5.90-6.10(m,2H), 7.00(s,2H) |
| MeN-CHMe(Et) | Me | Me | Me | 0.87(t,3H), 1.29(d,3H), 1.4.-1.8(m,3H), 1.82(s,3H), 1.86(s,3H), 1.95(s,3H), 2.35(s,3H), 2.37(s,3H), 2.47(s,3H), 3.02(s,3H), 4.34(m,1H), 6.99(s,2H) |
| $N(CH_2CH_2OH)_2$ | Me | Me | Me | 1.59(brs,2H), 1.81(s,6H), 1.94(s,3H), 2.34(s,3H), 2.39(s,3H), 3.80-3.95(m,8H), 6.98(s,2H) |
| $HO(CH_2)_3N(CH_2)_2OH$ | Me | Me | Me | 1.80(s,6H), 1.93(s,3H), 1.90-2.00(m,2H), 2.33(s,3H), 2.39(s,3H), 2.43(s,3H), 3.65(t,2H), 3.70-3.85(m,2H), 3.89(m,2H), 6.98(s,2H) |
| $(n\text{-}Bu)N(CH_2CH_2OMe)$ | Me | Me | H | 0.91(t,3H), 1.31(m,2H), 1.67(m,2H), 1.90(s,6H), 2.32(s,3H), 2.41(s,3H), 2.42(s,3H), 3.36(s,3H), 3.60-3.70(m,4H), 3.82(t,2H), 6.56(s,1H), 6.95(s,2H) |

| B | $R_3$ | $R_4$ | $R_6$ | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|---|
| p-Me-Ph$CH_2N(CH_2)_3OH$ | Me | Me | H | 1.80(m,2H), 1.90(s,6H), 2.20(s,3H), 2.30(s,3H), 2.34(s,3H), 2.49(s,3H), 3.54(t,2H), 3.82(t,2H), 4.90(s,2H), 6.58(s,1H), 6.95(s,2H), 7.10-7.25(m,4H) |
| EtN(n-Pr) | Me | Et | Et | 0.93(t,6H), 1.1-1.3(m,6H), 1.68(m,2H), 1.88(s,6H), 2.36(s,3H), 2.42(q,2H), 2.49(s,3H), 2.80(q,2H), 3.49(t,2H), 3.58(q,2H), 6.99(s,2H) |
| EtN(n-Bu) | H | Me | Me | 0.91(t,3H), 1.23(t,3H), 1.30(m,2H), 1.62(m,2H), 1.89(s,6H), 2.30(s,3H), 2.44(s,3H), 3.58(t,2H), 3.65(q,2H), 6.67(s,1H), 6.95(s,2H), 8.29(s,1H) |
| EtN(n-Pr) (HCl salt) | Me | Me | H | 0.93(t,3H), 1.25(t,3H), 1.70(m,2H), 1.91(s,6H), 2.33(s,3H), 2.42(s,3H), 3.55(m,2H), 3.69(m,2H), 6.58(s,1H), 6.96(s,2H) |
| $N(n\text{-}Pr)_2$ | Me | Me | H | 0.90(t,6H), 1.65(m,4H), 1.90(s,3H), 2.30(s,3H), 2.40(s,3H), 2.45(s,3H), 3.5-3.6(m,4H), 6.55(s,1H), 6.93(s,2H) |
| $N(CH_2CH{=}CH_2)_2$ | Me | Me | H | 1.90(s,6H), 2.30(s,3H), 2.40(s,3H), 2.48(s,3H), 4.20(d,4H), 5.15-5.30(m,4H), 5.09-6.10(m,2H), 6.55(s,1H), 6.95(s,2H) |
| $EtN(CH_2CH(CH_3)_2)$ | Me | Me | H | 0.95(t,3H), 1.23(t,3H), 1.95(s,6H), 2.11(m,1H), 2.35(s,3H), 2.46(s,3H), 2.50(s,3H), 3.44(d,2H), 3.68(q,2H), 6.59(s,1H), 6.98(s,2H) |
| $EtN(CH_2C(Me){=}CH_2)$ | Me | Me | H | 1.21(t,3H), 1.73(d,3H), 1.93(s,6H), 2.34(s,3H), 2.42(s,3H), 2.48(s,3H), 3.63(q,2H), 4.18(s,2H), 4.95(s,1H), 5.05(s,1H), 6.58(s,1H), 6.97(s,2H) |
| $EtN(CH_2)_2N(CH_3)_2$ | Me | Me | H | 1.26(t,3H), 1.88(s,6H), 2.31(s,3H), 2.34(s,6H), 2.41(s,3H), 2.43(s,3H), 2.62(m,2H), 3.64(q,2H), 3.74(m,2H), 6.55(s,1H), 6.94(s,2H) |
| $EtN(CH_2C(Me)_2)$ | Me | Me | Me | 0.91(d,6H), 1.17(t,3H), 1.84(s,6H), 1.95(s,3H), 2.05(m,1H), 2.35(s,3H), 2.38(s,3H), 2.47(s,3H), 3.36(d,2H), 3.61(q,2H), 6.98(s,2H) |

| B | $R_3$ | $R_4$ | $R_6$ | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|---|
| NH-$CHEt_2$ | Me | Me | Me | 0.96(t,6H), 1.5-1.8(m,4H), 1.82(s,6H), 1.87(s,3H), 2.3(s,3H), 2.39(s,3H), 2.40(s,3H), 4.30(m,1H), 4.76(d,1H,NH), 6.94(s,2H) |
| NH-$CHEt_2$ | Me | Me | H | 0.98(t,6H), 1.5-1.8(m,4H), 1.92(s,6H), 2.32(s,3H), 2.45(s,3H), 2.46(s,3H), 4.32(m,1H), 4.82(d,1H,NH), 6.44(s,1H), 6.95(s,2H) |
| NHCH(n-$Pr)_2$ | Me | Me | Me | 0.94(s,6H), 1.3-1.7(m,4H), 1.84(s,6H), 1.89(s,3H), 2.32(s,3H), 2.39(s,3H), 2.41(s,3H), 4.46(s,1H), 4.73(s,1H,NH), 6.96(s,2H) |
| NHCH(Me)(n-Bu) | Me | Me | Me | 0.92(t,3H), 1.27(d,3H), 1.37(m,4H), 1.5-1.7(m,2H), 1.83(s,6H), 1.84(s,3H), 1.89(s,3H), 2.33(s,3H), 2.40(s,3H), 2.43(s,3H), 4.41(m,1H), 4.77(d,1H,NH), 6.96(s,2H) |
| NH(n-Bu) | Me | Me | H | 0.98(t,3H), 1.35-1.45(m,2H), 1.5-1.7(m,2H), 1.90(s,6H), 2.30(s,3H), 2.43(s,3H), 2.44(s,3H), 3.57(q,2H), 4.90(m,t,1H, NH), 6.38(s,1H), 6.93(s,2H) |
| NHEt | Me | Me | H | 1.30(t,3H), 1.90(s,6H), 2.30(s,3H), 2.44(s,3H), 2.46(s,3H), 3.62(m,2H), 4.90(t,1H,NH), 6.40(s,1H), 6.93(s,2H) |
| NH-cyclopropyl | Me | Me | Me | 0.57(m,2H), 0,85(m,2H), 1.81(s,6H), 1.87(s,3H), 2.31(s,3H), 2.34(s,3H), 2.48(s,3H), 3.00(m,1H), 5.17(s,1H), 6.95(s,2H) |
| NH-(R)-CH(Et)($CH_2$OH) | Me | Me | Me | 1.05(t,3H), 1.5-1.8(m,2H), 1.80(s,6H), 1.89(s,3H), 2.31(s,3H), 2.40(s,6H), 3.84(2sets of ABq. 2H), 3.96(m,1H), 5.14(d,1H,NH), 6.95(s,2H), 7.04(s,1H) |
| NHCH(Me)(Et) | Me | Me | Me | 0.99(t,3H), 1.25(d,3H), 1.57(m,2H), 1.82(s,6H), 1.88(s,3H), 2.31(s,3H), 2.39(s,3H), 2.41(s,3H), 4.35(m,1H), 4.78(d,1H,NH), 6.94(s,2H) |

| B | $R_3$ | $R_4$ | $R_6$ | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|---|
| NH-(S)-CH(Et)($CH_2OH$) | Me | Me | Me | 1.05(t,3H), 1.5-1.8(m,2H), 1.80(s,6H), 1.89(s,3H), 2.31(s,3H), 2.40(s,6H), 3.84(2sets of ABq, 2H), 3.96(m,1H), 5.14(d,1H,NH), 6.95(s,2H), 7.04(s,1H) |
| NH-cyclopentyl | Me | Me | Me | 1.49(m,2H), 1.67(m,2H), 1.81(s,6H), 1.87(s,3H), 2.13(m,2H), 2.31(s,3H), 2.37(s,3H), 2.42(s,3H), 4.58(m,1H), 4.93(d,1H,NH), 6.94(S,2H) |
| NH-(S)-CH(Et)($CH_2OH$) | Me | Me | H | 1.08(t,3H), 1.5-1.8(m,2H), 1.89(s,6H), 2.30(s,3H), 2.43(s,3H), 2.448(s,3H), 2.453(s,3H), 3.86(2sts of ABq,2H), 3.98(m,1H), 5.17(d,1H,NH), 6.48(s,1H), 6.81(s,1H), 6.94(s,1H) |
| NH-(S)-CH(Et)($CH_2OMe$) | Me | Me | H | 0.98(t,3H), 1.6-1.8(m,2H), 1.90(s,3H), 1.91(s,3H), 2.30(s,3H), 2.42(s,3H), 2.44(s,3H), 3.39(s,3H), 3.53(2 sets of ABq,2H), 4.46(m,1H), 5.24(d,1H,NH), 6.42(s,1H), 6.92(s,2H) |
| NHCH(Me)(Et) | Me | Me | H | 0.99(t,3H), 1.26(d,3H), 1.5-1.7(m,2H), 1.91(s,6H), 2.30(s,3H), 2.44(s,6H), 4.34(m,1H), 4.79(d,1H,NH), 6.42(s,1H), 6.93(s,2H) |
| NH-(R)-CH(Et)($CH_2OMe$) | Me | Me | Me | 1.00(t,3H), 1.55-1.8(m,2H), 1.82(s,6H), 1.87(s,3H), 2.31(s,3H), 2.38(s,3H), 2.39(s,3H), 3.39(s,3H), 3.54(m,2H), 4.45(m,1H), 5.25(d,1H,NH), 6.94(s,2H) |
| NH-(S)-CH(Et)($CH_2OMe$) | Me | Me | Me | 1.00(t,3H), 1.55-1.8(m,2H), 1.82(s,6H), 1.87(s,3H), 2.31(s,3H), 2.38(s,3H), 2.39(s,3H), 3.39(s,3H), 3.54(m,2H), 4.45(m,1H), 5.25(d,1H,NH), 6.94(s,2H) |

| B | $R_3$ | $R_4$ | $R_6$ | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|---|
| NH-$CH_2$CH(Me)(Et) | Me | Me | Me | 0.96(t,3H), 1.00(d,3H), 1.1-1.3(m,2H), 1.4-1.6(m,2H), 1.6-1.8(m,1H), 1.82(s,6H), 1.88(s,3H), 2.31(s,3H), 2.39(s,3H), 2.42(s,3H), 3.40(m,1H), 3.54(m,1H), 5.00(t,1H,NH), 6.94(s,2H) |
| NH-(S)-CH($CH_2$Ph)($CH_2$OH) | Me | Me | Me | 1.77(s,3H), 1.78(s,3H), 1.82(s,3H), 1.99(s,3H), 2.30(s,3H), 2.41(s,3H), 2.84(m,1H), 3.12(m,1H), 3.75(m,1H), 3.93(m,1H), 4.27(m,1H), 5.15(d,1H,NH), 6.94(s,2H), 7.2-7.4(m,5H) |
| NH-(R)-CH($CH_2$Ph)($CH_2$OH) | Me | Me | Me | 1.77(s,3H), 1.78(s,3H), 1.82(s,3H), 1.99(s,3H), 2.30(s,3H), 2.41(s,3H), 2.84(m,1H), 3.12(m,1H), 3.75(m,1H), 3.93(m,1H), 4.27(m,1H), 5.15(d,1H,NH), 6.94(s,2H), 7.2-7.4(m,5H) |
| NH-(S)-CH($CH_2$Ph)($CH_2$OMe) | Me | Me | Me | 1.80(s,3H), 1.83(s,3H), 1.88(s,3H), 2.31(s,3H), 2.33(s,3H), 2.44(s,3H), 2.90(m,1H), 3.13(m,1H), 3.40(s,3H), 3.44(m,2H), 4.70(m,1H), 5.35(d,1H,NH), 6.95(s,2H), 7.2-7.4(m,5H) |
| NH-(R)-CH($CH_2$Ph)($CH_2$OMe) | Me | Me | Me | 1.80(s,3H), 1.83(s,3H), 1.88(s,3H), 2.31(s,3H), 2.33(s,3H), 2.44(s,3H), 2.90(m,1H), 3.13(m,1H), 3.40(s,3H), 3.44(m,2H), 4.70(m,1H), 5.35(d,1H,NH), 6.95(s,2H), 7.2-7.4(m,5H) |
| NH-(S)-CH(Et)($CH_2$OEt) | Me | Me | H | 1.00(t,3H), 1.20(t,3H), 1.6-1.8(m,2H0, 1.90(s,3H), 1.91(s,3H), 2.30(s,3H), 2.42(s,3H), 2.43(s,3H), 3.4-3.6(m,2H), 4.41(m,1H), 5.34(d,1H,NH), 6.42(s,1H), 6.93(s,2H) |
| NH$CH_2$CH(n-Bu)(Et) | Me | Me | Me | 0.89(t,3H), 0.95(t.3H), 1.2-1.4(m,7H), 1.54-1.62(m.1H), 1.82(s,6H), 1.88(s.3H), 2.31(s,3H), 2.39(s,3H), 2.42(s.3H), 3.53(m.2H), 4.90(m.1H), 6.95(s.2H) |




| $NR_1R_2$ | $R_4$ | $R_6$ | $R_5$ |
|---|---|---|---|
| | $^1$H-NMR($CDCl_3$) $\delta$ (ppm) | | |
| EtN(n-Bu) | Me | Me | 2,4-dimethylphenyl |
| | 0.89(t,3H), 1.15(t,3H), 1.30(m,2H), 1.2-1.4(m,2H), 1.87(s,3H), 1.97(s,3H), 2.33(s,3H), 2.37(s,3H), 2.44(s,3H), 3.49(t,2H), 3.55(q,2H), 6.9-7.2(m,3H) | | |
| $N(n\text{-}Pr)_2$ | Me | Me | 2,4-dimethylphenyl |
| | 0.86(t,6H), 1.62(m,4H), 1.87(s,3H), 1.97(s,3H), 2.34(s,3H), 2.37(s,3H), 3.48(m,4H), 6.95-7.20(m,3H) | | |
| EtN(n-Bu) | Me | Me | 2,6-dimethylphenyl |
| | 0.89(t,3H), 1.31(t,3H), 1.31(m,2H), 1.62(m,2H), 1.86(s,3H), 1.90(s,3H), 2.35(s,3H), 2.43(s,3H), 3.50(t,2H), 3.56(q,2H), 7.1-7.2(m,3H) | | |
| EtN(n-Pr) | Me | Me | 2,4-dimethylphenyl |
| | 0.89(t,3H), 1.18(t,3H), 1.66(m,2H), 1.86(s,6H), 1.91(s,3H), 2.35(s,3H), 2.43(s,3H), 3.43(m,2H), 3.56(m,2H), 7.0-7.2(m,3H) | | |
| EtN(n-Bu) | Me | H | 2,5-dimethylphenyl |
| | 0.93(t,3H),1.22(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 2.04(s,6H), 2.33(s,3H), 2.41(s,3H), 2.42(s,3H), 3.58(t,2H), 3.64(q,2H), 6.70(s,1H), 7.06(s,1H), 7.1-7.25(m,2H) | | |
| EtN(n-Bu) | Me | H | 3-methyl-4-chlorophenyl |
| | 0.94(t,3H), 1.23(t,3H), 1.23-1.45(m,2H), 1.4-1.6(m,2H), 2.43(s,3H), 2.44(s,3H), 2.58(s,3H), 3.4-3.75(m,4H), 6.94(s,1H), 7.4-7.65(m,3H) | | |
| EtN(n-Bu) | Me | H | 2.6-dimethyl-4-bromophenyl |

| $NR_1R_2$ | $R_4$ | $R_5$ | $R_5$ |
|---|---|---|---|
| | $^1$H-NMR($CDCl_3$) $\delta$ (ppm) | | |
| | 0.92(t,3H), 1.22(t,3H), 1.25-1.40(m,2H), 1.55-1.60(m,2H), 1.91(s,6H), 2.40(s,3H), 2.43(s,3H), 3.57(m,2H), 3.64(q,2H), 6.50(s,1H), 7.27(s,2H) | | |
| EtN(n-Bu) | Me | H | 2,4-dimethyl-6-bromophenyl |
| | 0.98(t,3H), 1.28(T,3H), 1.3-1.5(m,2H), 1.6-1.8(M,2H), 2.00(s,3H), 2.36(s,3H), 2.48(s,3H), 2.53(s,3H), 3.64(t,2H), 3.71(q,2H), 6.63(s,1H), 7.09(d,1H), 7.38(d,1H) | | |
| $NHCH(Et)_2$ | Me | H | 2,6-dimethyl-4-bromophenyl |
| | 0.98(t,6H), 1.5-1.8(m,4H), 1.94(s,6H), 2.44(s,3H), 2.45(s,3H), 4.30(M,1H), 4.80(d,1H,NH), 6.39(S,1H), 7.28(s,2H) | | |
| $NHCH(Et)(CH_2OH)$ (S)-isomer | Me | H | 2,6-dimethyl-4-bromophenyl |
| | 1.07(t,3H), 1.5-1.8(m,2H), 1.90(s,6H), 2.42(s,3H), 2.44(s,3H), 3.5-3.8(m,2H), 3.87(m,1H), 5.18(d,1H,NH), 6.45(s,1H), 6.56(s,1H), 7.27(s,2H) | | |
| $NHCH(Et)(CH_2OMe)$ | Me | H | 2,6-dimethyl-4-bromophenyl |
| | 1.00(t,3H), 1.55-1.75(m,2H), 1.92(s,6H), 2.42(s,3H), 2.43(s,3H), 3.39(s,3H), 3.55(2 sets of ABq,2H), 4.46(m,1H), 5.28(d,1H,NH), 6.38(s,1H), 7.26(s,2H) | | |
| $NHCH(Et)(CH_2OH)$ | Me | H | 2,6-dimethyl-4-chlorophenyl |
| | 1.07(t,3H), 1.55-1.80(m,2H), 1.91(s,6H), 2.42(s,3H), 2.45(s,3H), 3.74(2 sets of ABq,2H), 4.00(m,1H), 5.18(d,1H,NH), 6.46(s,1H), 6.60(brs,1H), 7.11(s,2H) | | |
| $NH\text{-}CH(Et)(CH_2OH)$ (R)-isomer | Me | H | 2,6-dimethyl-4-bromophenyl |
| | 1.07(t,3H), 1.55-1.75(m,2H), 1.90(s,6H), 2.42(s,3H), 2.44(s,3H), 3.75(2 sets of ABq,2H), 4.00(m,1H), 5.14(d,1H,NH), 6.45(s,1H), 6.50(brs,1H), 7.27(s,2H) | | |

EXAMPLE 7

A. 1-[2-Amino-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-3-yl]-2-ethyl-butan-1-one

A mixture of 3-hydroxy-2-butanone (0.637 g, 7.23 mmol), 2,4,6-trimethylaniline (0.973 g, 7.19 mmol) and p-toluenesulfonic acid (0.012 g, 0.06 mmol) in 15 ml of

benzene was refluxed using a Dean-Stark trap to remove water. After 3 hours, 4-ethyl-3-oxo-hexanenitrile (1.008 g, 0.724 mmol) was added and the mixture was refluxed for an additional 15 hours until all the starting material was consumed. The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was dried and concentrated to give 1.679 g of brown oil which was purified by silica gel column chromatography to give 368 mg of the title compound as a brown oil and 732 mg of undesired 2-(2-ethyl-butyl)-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrole-3-carbonitrile as a yellow solid. $^1$H-NMR ($CDCl_3$) (the title compound) $\delta$ 0.94(t,6H), 1.4-1.8(m,4H), 1.73(s,3H), 1.98(s,6H), 2.25(s,3H). 2.34(s,3H), 3.00(m,1H), 5.80(brs,2H), 6.99(s,2H) ppm. $^1$H-NMR ($CDCl_3$) (2-(2-ethyl-butyl)-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrole-3-carbonitrile)$\delta$0.85(t,6H),1.5-1.85(m,4H), 1.71(s,3H), 1.88(s,6H), 1.95-2.10(m,1H), 2.14(s,3H), 2.34(s,3H), 6.96(s,2H) ppm.

B. N-[3-(2-ethyl-butyryl)-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-2-yl]-acetamide

A mixture of 1-[2-amino-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-3-yl]-2-ethyl-butan-1-one (326 mg, 1 mmol) and acetic anhydride (108 mg, 1.05 mmol) in 3 ml of acetic acid was heated to reflux for 2 hours. The mixture was cooled, quenched with water, neutralized with saturated potassium carbonate, and extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated to give the title compound as a dark oil. The oil was purified through silica gel column chromatography to give 107 mg of the title compound as a brown oil. $^1$H-NMR ($CDCl_3$) $\delta$ 0.88(t,6H), 1.4-1.8(m,4H), 1.76(s,3H), 1.88(s,3H), 1.93(s,6H), 2.25(s,3H). 2.28(s,3H), 2.98(m,1H), 6.89(s,2H) ppm.

C. 4-(1-Ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of N-[3-(2-ethyl-butyl)-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-2-yl]-acetamide (100 mg, 0.27 mmol), ammonium chloride (290 mg. 5.42 mmol). and acetamide (1.635 g) was heated to reflux for 2 hours. The mixture was cooled. quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 56 mg of the title compound as a dark oil. The oil was purified through silica gel column chromatography to give the title compound as a yellow oil. $^1$H-NMR ($CDCl_3$) $\delta$ 0.85(t,6H), 1.70-2.0(m,4H), 1.83(s,6H), 1.99(s,3H 2.36(s,3H). 2.44(s,3H). 2.61(s,3H), 3.26(m,1H). 7.00(s,2H) ppm.

EXAMPLE 8

Butyl-ethyl-[2,5-dimethyl-7-(2,6-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]amine and 4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethyl-benzoic acid

A solution of 7-(4-bromo-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-butyl-ethyl-amine (0.700 g, 1.63 mmol) in 5 ml of dry tetrahydrofuran (THF) was added to a cooled solution of n-butyl lithium (n-BuLi) (2.5 M in hexane, 1.79 mmol) in 5 ml of dry THF at -78°C and stirred at that temperature for 20 minutes.

A part (1 mL) was taken from the reaction mixture and was quenched with an excess of water and extracted with ethyl acetate, dried and concentrated to give butyl-ethyl-[2,5-dimethyl-7-(2,6-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]amine as a clear oil. The oil was treated with 1 N HCl in methanol and concentrated to dryness. The residue was recrystallized from ethyl acetate to give the corresponding HCl salt as white crystals, mp 148-150°C.

The rest of the reaction mixture was quenched with an excess of dry ice at -78°C and the -78°C bath was removed. After 30 minutes, tlc showed that no starting material was left, and the mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give an off-white solid (0.550 g). The solid was recrystallized from 2-propanol to give the second title compound as white crystals, mp 228-230°C.

EXAMPLE 9

4-[4-(Butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethyl-benzoic acid methyl ester

A mixture of 4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethyl-benzoic acid (0.230g, 0.583 mmol) in 40 ml of 1 N HCl and methanol was heated at reflux for 3 hours (tlc showed that all starting materials were consumed). The mixture was concentrated to dryness. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried and concentrated to give the title compound as a light brown oil. The oil was purified through silica gel column chromatography using 5% ethyl acetate in hexane as an eluent to give a golden oil. The corresponding HCl salt was prepared as an off-white solid, mp 58-60°C.

EXAMPLE 10

[4-(Butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethylphenyl}-methanol

A solution of 4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethyl-benzaldehyde (0.100 g, 0.264 mmol) in 1 ml MeOH was treated with sodium borohydride (0.030 g, 0.793 mmol) and stirred at room temperature for 20 minutes. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to dryness to give a clear oil. The oil was purified through silica gel column chromatography to give the title compound (0.092 g, 92% yield) as a white solid, mp 93-95°C.

EXAMPLE 11

Butyl-ethyl-[7-(4-fluoromethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-amine

A solution of {4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethylphenyl}-methanol (0.071 g, 0.186 mmol) in 2 ml anhydrous methylene chloride was cooled to -78°C and treated with dimethylaminosulfur trifluoride (0.063g, 0.390 mmol) and stirred at room temperature for 1 hour. The mixture was quenched with water and extracted with chloroform. The organic layer was washed with brine, dried, and concentrated to give an oil which was purified through silica gel using 2% methanol/chloroform as eluent to give the title compound as an off-white solid, mp 163-165°C.

EXAMPLE 12

Butyl-ethyl-[7-(4-methoxymethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-amine

A solution of {4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethylphenyl}-methanol (0.100 g, 0.263 mmol) in 1 ml of dry tetrahydrofuran was treated with sodium hydride (0.0116 g, 0.289 mmol, 60% in oil). After stirring for 10 minutes, an excess of methyl iodide was added. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give an oil. The oil was purified through silica gel column using 10% ethyl acetate in hexane as eluent to give 0.081 g (78%) of the title compound as a white glass form.

EXAMPLE 13

[7-(4-aminomethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-butyl-ethyl-amine

A solution of 4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethyl-benzaldehyde (0.200 g, 0.528 mmol) in 2 ml of methanol was treated with sodium cyanoborohydride (0.023 g, 0.37 mmol), ammonium acetate (0.407 g, 5.28 mmol) and sodium sulfate. After stirring for 1 hour, the mixture was concentrated to remove methanol and the residue was dissolved in water, saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give an oil. The oil was purified through silica gel column using 10% methanol in chloroform as eluent to give the title compound as a clear oil. The corresponding di-HCl salt was prepared as a white solid, mp 158-160°C.

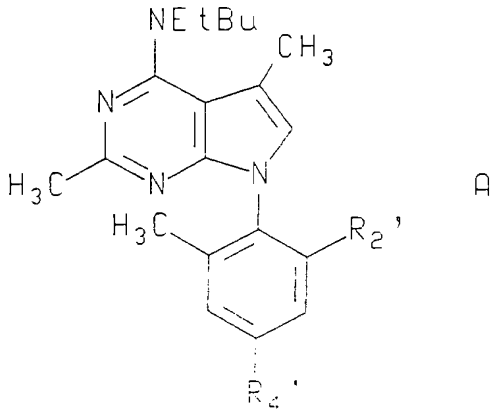
EXAMPLE 14

Butyl-ethyl-[7-(4-methoxyethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-amine

The title compound was prepared starting from the 1-{4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethyl-phenyl}-ethanol, sodium hydride and methyl iodide and employing the procedure of Example 12.

The $^1$H NMR data of the compounds prepared by the methods of Examples 8 to 15 as well as other compounds prepared by these methods are listed in the following Table.

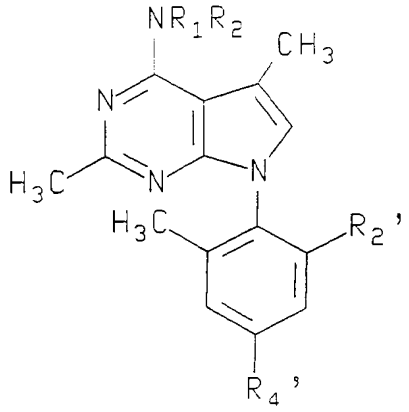
Table I




A

| Example | R2' | R4' | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|
| 8 | Me | H | 0.93(t,3H), 1.23(t,3H), 1.25-1.40(m,2H), 1.55-1.60(m,2H), 1.95(s,6H), 2.42(s,3H), 2.45(s,3H), 3.58(m,2H), 3.64(q,2H), 6.56(s,1H), 7.05-7.20(M,3H) |
| 8 | Me | COOH | 0.95(t,3H), 1.27(t,3H), 1.3-1.45(m,2H), 1.6-1.8(m,2H), 1.96(s,6H), 2.43(s,3H), 2.56(s,3H), 3.65(t,2H), 3.72(q,2H), 6.61(s,1H), 7.52(s,2H) |
| | Me | CHO | 0.92(t,3H), 1.23(t,3H), 1.25-1.40(m,2H), 1.55-1.70(m,2H), 2.03(s,6H), 2.42(s,3H), 2.43(s,3H), 3.58(m,2H), 3.64(q,2H), 6.54(s,1H), 7.65(s,2H), 9.99(s,1H) |
| 10 | Me | $CH_2OH$ | 0.92(t,3H), 1.22(t,3H), 1.25-1.40(m,2H), 1.55-1.70(m,2H), 1.94(s,6H), 2.41(s,3H), 2.45(s,3H), 3.58(t,2H), 3.65(q,2H), 4.55(s,2H), 6.54(s,1H), 7.09(s,2H) |
| | Me | CH(Me)(OH) | 0.91(t,3H), 1.21(t,3H), 1.2-1.4(m,2H), 1.44(d,3H), 1.5-1.7(m,2H), 1.91(s,6H), 2.39(s,3H), 2.42(s,3H), 3.57(t,2H), 3.64(q,2H), 4.75(q,1H), 6.53(s,1H), 7.11(s,1H), 7.13(s,1H) |
| 9 | Me | COOMe | 0.92(t,3H), 1.23(t,3H), 1.25-1.30(m,2H), 1.5-1.7(m,2H), 1.99(s,6H), 2.41(s,3H), 2.43(s,3H), 3.58(t,2H), 3.64(q,2H), 3.91(s,3H), 6.53(s,1H), 7.81(s,2H) |
| 11 | Me | $CH_2F$ | 0.90(t,3H), 1.20(t,3H), 1.24-1.40(m,2H), 1.5-1.7(m,2H), 1.95(s,6H), 2.38(s,3H), 2.42(s,3H), 3.54(t,2H), 3.62(q,2H). 4.30(d, 2H), 6.50(s,1H), 7.10(s,2H) |
| 13 | Me | $CH_2NH_2$ | 0.90(t,3H), 1.20(t,3H), 1.2-1.4(m,2H), 1.5-1.7(m,2H), 1.93(s,6H), 2.40(s,3H), 2.42(s,3H), 3.54(t,2H), 3.62(q,2H), 3.82(s,2H), 6.52(s,1H), 7.10(s,2H) |
| | Me | CONHMe | 0.94(t,3H), 1.2-1.4(m,5H), 1.4-1.6(m,2H), 1.96(s,6H), 2.43(s,3H), 2.75(s,1.5H), 2.82(s,1.5H), 3.24(s,1H), 3.5-3.8(m.4H), 6.53(s,1H), 7.22(s,1H), 7.48(s,1H) |
| | Me | OH | 0.89(t,3H), 1.20(t,3H), 1.2-1.4(m,2H), 1.5-1.7(m,2H), 1.76(s,6H), 2.379s,3H), 2.52(s,3H), 3.58(t,2H), 3.65(q,2H), 6.26(s,2H), 6.50(s,1H) |

| Example | R2' | R4' | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|
| | Me | I | 0.92(t,3H), 1.22(t,3H), 1.2-1.35(m,2H), 1.5-1.7(m,2H), 1.89(s,6H), 2.40(s,3H), 2.44(s,3H), 3.57(t,2H), 3.64(q,2H), 6.50(s,1H), 7.48(s,2H) |
| | Me | Et | 0.93(t,3H), 1.25(m,6H), 1.2-1.4(m,2H), 1.55-1.60(m,2H), 1.92(s,6H), 2.41(s,3H), 2.46(s,3H), 2.63(q,2H), 3.57(t,2H), 3.64(q,2H), 6.55(s,1H), 6.96(S,2H) |
| 14 | Me | CH(Me)(OMe) | 0.88(t,3H), 1.18(t,3H), 1.2-1.4(m,2H), 1.38(d,3H), 1.5-1.7(m,2H), 1.90(s,6H), 2.36(s,3H), 2.40(s,3H), 3.24(s,3H), 3.4-3.65(m,4H), 4.20(q,1H), 6.50(s,1H), 7.00(s,2H) |
| 12 | Me | $CH_2OMe$ | 0.92(t,3H), 1.22(t,3H), 1.2-1.4(m,2H), 1.5-1.65(m,2H), 1.94(s6H), 2.41(s,3H), 2.44(s,3H), 3.42(s,3H), 3.45-3.52(m,4H), 4.42(s,2H), 6.53(s,1H), 7.10(s,2H) |
| | Me | $C(Me)_2(OH)$ | 0.92(t,3H), 1.22(t,3H), 1.25-1.40(m,2H), 1.5-1.7(m,2H), 1.58(s,6H), 1.95(s,6H), 2.40(s,3H), 2.45(s,3H), 3.5-3.7(m,4H), 6.54(s,1H), 7.23(s,2H) |




| $NR_1R2$ | R2' | $R_{4'}$ | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|
| $NHCH(Et)_2$ | Me | H | 0.98(t,6H), 1.5-1.8(m,4H), 1.97(s,6H), 2.44(s,3H), 2.46(s,3H), 4.34(m,1H), 4.81(d,1H), 6.44(s,1H), 7.1-7.2(m,3H) |

| | | | |
|---|---|---|---|
| $NHCH(Et)_2$ | Me | CHO | 0.98(t,6H), 1.5-1.8(m,4H), 2.06(s,6H), 2.43(s,3H), 2.46(s,3H), 4.31(m,1H), 4.83(d,1H), 6.43(s,1H), 7.66(s,1H), 9.99(s,1H) |
| $NHCH(Et)(CH_2OMe)$ | Me | H | 1.01(t,3H), 1.4-1.6(m,2H), 1.95(s,6H), 2.42(s,3H), 2.44(s,3H), 3.40(s,3H), 3.55(2 sets of ABq,2H), 4.48(m,1H), 5.26(d,1H,NH), 6.43(s,1H), 7.0-7.2(m,3H) |

EXAMPLE 15

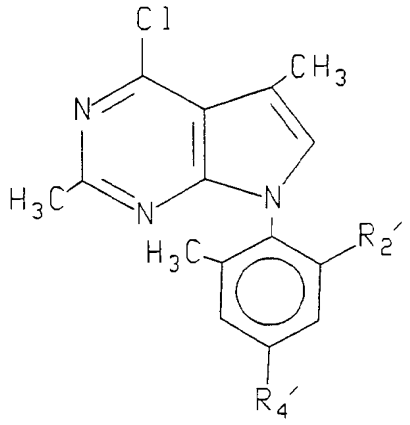
The following compounds of above formula A (Example 14) were prepared by procedures analogous to those in Examples 8 to 13.

| R2' | R4' | $^1H$ NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|
| H | Me | 0.95(t,3H), 1.23(t,3H), 1.2-1.4(m,2H), 1.55-1.77(m,2H), 2.08(s,3H), 2.38(s,3H), 2.44(s,3H), 2.50(s,3H)3.59(t,2H), 3.66(q,2H), 6.71(ws,1H), 7.0-7.2(m,3H) |
| CHO | Me | 0.95(t,3H), 1.26(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 2.05(s,3H), 2.438(s,3H), 2.443(s,3H), 2.448(s,3H), 3.5-3.8(m,4H), 6.7(s,1H), 7.39(d,1H), 7.68((d,1H), 9.33(s,1H) |
| $CH_2OH$ | Me | 0.96(t,3H), 1.27(t,3H), 1.25-1.45(m,2H), 1.6-1.75(m,2H), 1.95(s,3H), 2.41(s,3H), 2.43(s,3H), 2.44(s,3H), 3.5-3.8(m,4H), 4.15(m,2H), 6.6(s,1H), 7.11(s,1H), 7.26(s,1H) |
| $CH_2F$ | Me | 0.96(t,3H), 1.28(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 1.95(s,3H), 2.41(s,3H), 2.43(s,3H), 2.46(s,3H), 3.5-3.8(m,4H), 5.01(2 sets of ABq,2H), 6.63(s,1H), 7.15(s,1H), 7.25(s,1H) |
| CH(Me)(OH) | Me | 0.96(t,3H), 1.27(t,3H), 1.25-1.409m,2H), 1.43(d,3H), 1.6-1.8(m,2H), 1.93(s,3H), 2.42(s,6H), 2.45(s,3H), 3.4-3.8(m,4H), 4.37(q,2H), 5.10(s,1H), 6.62(s,1H), 7.09(s,1H), 7.35(s,1H) |

| R2' | R4' | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|
| I | Me | 0.96(t,3H), 1.27(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 1.97(s,3H), 2.34(s,3H), 2.46(s,3H), 2.50(s,3H), 3.5-3.8(m,4H), 6.58(s,1H), 7.10(S,1H), 7.62(s,1H) |
| Cl | Me | 0.95(t,3H), 1.25(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 1.97(s,3H), 2.36(s,3H), 2.44(s,3H), 2.48(s,3H), 3.5-3.8(m,4H), 6.61(s,1H), 7.04(s,1H), 7.19(s,1H) |
| $C(Me)_2(OH)$ | Me | 0.94(t,3H), 1.18(s,3H), 1.25(t,3H), 1.25-1.5(m,2H), 1.55(s,3H), 1.6-1.8(m,2H), 1.69(s,3H), 2.38(s,3H), 2.42(s,3H), 2.43(s,3H), 3.5-3.8(m,4H), 4.13(brs,1H), 6.57(s,1H), 7.04(s,1H), 7.39(s,1H) |
| $CH_2NH_2$ | Me | 0.96(t,3H), 1.26(t,3H), 1.3-1.5(m,2H), 1.6-1.8(M,2H), 1.85(s,3H), 2.28(S<3H), 2.38(s,6H), 3.28(q,2H), 3.5-3.8(m,4H), 6.58(s,1H), 6.93(s,1H), 6.99(s,1H) |
| $CH_2OMe$ | Me | 0.96(t,3H), 1.26(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 1.92(s,3H), 2.38(s,3H), 2.44(s,3H), 2.46(s,3H), 3.25(s,3H), 3.61(t,2H), 3.68(q,2H), 4.04(ABq,2H), 6.62(s,1H), 7.06(s,1H), 7.22(s,1H) |
| Et | Me | 0.95(t,3H), 1.04(t,3H), 1.26(t,3H), 1.25-1.45(m,2H), 1.90(s,3H), 2.15-2.35(m,2H), 2.37(s,3H), 2.44(s,3H), 2.47(s,3H), 3.63(m,2H), 3.67(q,2H), 6.57(s,1H), 6.98(s,1H), 7.01(s,1H) |
| CH(Me)(OMe) | Me | 0.96(t,3H), 1.2-1.4(m,6H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 1.91(s,3H), 2.41(s,3H), 2.43(s,3H), 2.44(s,3H), 3.14(s,3H), 3.5-3.75(m,4H), 3.81(q,1H), 6.54(s,1H), 7.06(s,1H), 7.25(s,1H) |

Example 16

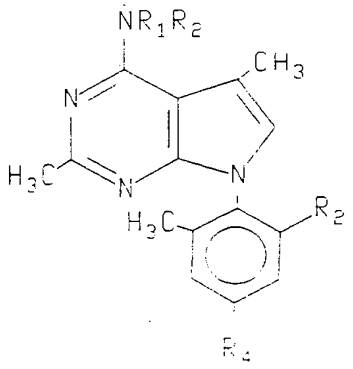
A. The following compounds were prepared by the procedures analogous to those in Examples 8 to 13 starting from n-BuLi with 4-chloro-2,5-dimethyl-7-(2,6-dimethyl-4-bromo- or 2,4-dimethyl-6-bromo-phenyl)-7H-pyrrolo-[2,3-d]pyrimidine, followed by quenching with an appropriate electrophile compound.



| $R^{2'}$ | $R^{4'}$ | $^1H$ NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|
| Me | Et | 1.25(t,3H), 1.89(s,6H), 2.50(s,3H), 2.63(s,3H), 2.62(m,2H), 6.78(s,1H), 6.99(s,2H) |
| Me | OH | 1.79(s,6H), 2.50(s,3H), 2.74(s,3H), 6.36(s,2H), 6.80(s,1H), 8.60(s,1H) |
| Me | $C(Me_2)(OH)$ | 1.60(s,6H), 1.93(s,6H), 2.50(s,3H), 2.63(s,3H), 6.78(s,1H), 7.23(s,1H) |
| $CH_2F$ | Me | 1.92(s,3H), 2.43(s,3H), 2.52(s,3H), 2.53(s,3H), 4.87(ABq,1H), 5.11(ABq,1H), 6.87(s,1H), 7.26(s,1H), 7.27(s,1H) |
| Et | Me | 1.01(t,3H), 1.87(s,3H), 2.20(q,2H), 2.38(s,3H), 2.53(s,3H), 2.65(s,3H), 6.81(s,1H), 7.01(s,1H), 7.04(s,1H) |
| $C(Me_2)(OH)$ | Me | 1.26(s,3H), 1.43(s,3H), 1.66(s,3H), 2.40(s,3H), 2.52(s,3H), 2.62(s,3H), 6.83(s,1H), 7.07(s,1H), 7.45(s,1H) |
| H | Me | 2.04(s,3H), 2.40(s,3H), 2.51(s,3H), 2.67(s,3H), 6.92(s,1H), 7.13(s,2H), 7.18(s,1H) |

| $R^{2'}$ | $R^{4'}$ | $^1H$ NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|
| CHO | Me | 2.00(s,3H), 2.47(s,3H), 2.54(s,3H), 2.63(s,3H), 6.92(s,1H), 7.45(m,1H), 7.70(m,1H), 9.39(s,1H) |
| $CH_2OH$ | Me | 1.88(s,3H), 2.36(s,3H), 2.50(s,3H), 2.57(s,3H), 3.56(brs,1H), 4.05-4.25(m,2H), 6.84(s,1H), 7.08(s,1H), 7.25(s,1H) |

B. The following compounds were prepared starting with the appropriate amine and the appropriate 4-chloro-2,5-dimethyl-7-(substituted phenyl)-7H-pyrrolo[2,3-d]pyrimidine (compounds listed in the table above under 16A or other related compounds) in DMSO and employing the general procedure of Example 5.




| $NR_1R_2$ | $R_2'$ | $R_4'$ | $^1H$ NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|
| NH-(S)-CH(Et)($CH_2OH$) | Me | Et | 1.07(t,3H), 1.23(t,3H), 1.45-1.56(m,2H), 1.90(s,3H), 1.91(s,3H), 2.43(s,3H), 2.45(s,3H), 2.60(q,2H), 3.65(m,1H), 3.83(m,1H), 4.00(m,1H), 5.17(d,1H), 6.49(s,1H), 6.95(s,2H) |
| NH-(S)-CH(Et)($CH_2OH$) | Et | Me | 1.00(t,3H), 1.07(t,3H), 1.6-1.85(m,2H), 1.88(s,3H), 2.15-2.30(m,2H), 2.32(s,3H), 2.42(s,3H), 2.48(s,3H), 3.6-3.9(m,2H), 3.92-4.10(m,1H),5.25(d,1H), 6.5(s,1H), 6.94(s,1H), 7.0(s,1H) |

| $NR_1R_2$ | $R_2'$ | $R_4'$ | $^1H$ NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|
| NH-(S)-CH(Et)($CH_2OH$) | Me | $CMe_2OH$ | 1.08(t,3H), 1.58(s,6H), 1.6-1.9(m,2H), 1.94(s,3H), 1.95(s,3H), 2.46(s,3H), 2.50(s,3H), 3.5-3.95(m,2H), 4.2(brs ,1H), 5.28(brs,1H), 6.53(s,1H), 7.24(s,2H) |
| NH-(S)-CH(Et)($CH_2OH$) | C(OH)($Me_2$) | Me | 1.11(t,3H), 1.24(s,3H), 1.5-1.9(m,2H), 1.50(s,0.5x3H), 1.53(0.5x3H), 1.71(s,3H), 2.39(s,3H), 2.43(s,3H), 2.48(s,3H), 3.16(brs,0.5H), 3.29(brs,0.5H), 3.6-3.95(m,2H), 3.95-4.10(m,1H), 5.2-5.3(m,1H), 6.54(s,1H), 7.05(s,1H), 7.40(s,0.5H), 7.43(s,0.5H) |
| NH-(S)-CH(Et)($CH_2OH$) | H | Me | 1.10(t,3H), 1.5-1.9(m,2H), 2.05(s,3H), 2.37(s,3H), 2.48(s,6H), 3.6-3.9(m,2H), 3.9-4.1(m,1H), 5.23(d,1H), 6.64(s,1H), 7.0-7.2(m,2H) |
| NH-(S)-CH(Et)($CH_2OH$) | CHO | Me | 1.09(t,3H), 1.55-1.90(m,2H), 2.02(s,3H), 2.42(s,6H), 2.47(s,3H), 3.6-3.9(m,2H), 4.0-4.15(m,1H), 5.27(t,1H), 6.62(s,1H), 7.39(s,1H), 7.65(s,1H), 9.36(s,1H) |
| NH-(S)-CH(Et)($CH_2OH$) | $CH_2OH$ | Me | both diastereoisomers were separated by column chromatography and showed identical spectra. 1.11(t,3H), 1.55-1.90(m,2H), 1.95(s,3H), 2.40(s,3H), 2.43(s,3H), 2.49(s,3H), 3.6-3.95(m,2H), 4.0-4.3(m,2H), 4.4(brs,1H), 5.30(d,1H), 6.57(s,1H), 7.11(s,1H), 7.27(s,1H) |
| NH-(S)-CH(Et)($CH_2OH$) | $CH_2F$ | Me | 1.11(t,3H), 1.5-1.85(m,2H), 1.94(s,3H), 2.41(s,3H), 2.45(s,3H), 2.47(s,3H), 3.6-3.9(m,2H), 4.0-4.2(m,1H), 4.75-5.25(m,2H), 5.24(m,1H), 6.58(s,1H), 7.16(s,1H), 7.24(s,1H) |

Example 17

The following compounds were prepared by the procedures analogous to those in Examples 8 to 13 starting from an excess of n-BuLi with 4-substituted amino-2,5-dimethyl-7-(2,4,6-tri-substituted-phenyl)-7H-pyrrolo-[2.3-d]pyrimidine, followed by quenching with an appropriate electrophile.

| $NR_1R_2$ | $R_2'$ | $R_4'$ | $^1H$ NMR ($CDCl_3$) $\delta$ |
|---|---|---|---|
| NH-(S)-CH(Et)($CH_2OH$) | $CH_2CH_2OH$ | Me | 1.11(t,3H), 1.5-1.9(m,2H), 1.84(s,3H), 2.37(s,3H), 2.45(s,3H), 2.48(s,3H), 2.45-2.65(m,2H), 3.6-3.95(m,4H), 4.15(m,1H), 5.28(d,1H), 6.54(s,1H), 7.02(s,1H), 7.09(s,1H) |
| NH-(S)-CH(Et)($CH_2OH$) | Me | CHO | 1.08(t,3H), 1.5-1.8(m,2H), 2.02(s,6H), 2.42(s,3H), 2.46(s,3H), 3.6-3.9(m,2H), 4.0(brs,1H), 5.20(d,1H), 6.49(s,1H), 7.65(s,2H), 9.98(s,1H) |
| NH-(S)-CH(Et)($CH_2OH$) | Me | I | 1.06(t,3H), 1.6-1.9(m,2H), 1.88(s,6H), 2.42(s,3H), 2.44(s,3H), 3.6-3.9(m,2H), 4.08(brs,1H), 5.20(d,1H), 6.45(s,1H), 7.48(s,2H) |
| NH-(S)-CH(Et)($CH_2OH$) | Me | $CH_2OH$ | 1.08(t,3H), 1.6-1.85(m,2H), 1.93(s,6H), 2.45(s,6H), 3.6-3.95(m,2H), 4.10(brs,1H), 4.60(s,2H), 5.24(brs,1H), 6.50(s,1H), 7.11(s,2H) |
| NH-(S)-CH(Et)($CH_2OH$) | Me | C(Me)-($C=CH_2$) | 1.08(t,3H), 1.5-1.8(m,2H), 1.94(s,6H), 2.13(s,3H), 2.44(s,3H), 2.45(s,3H), 3.55-3.90(m,2H), 4.00(brs,1H), 5.07(s,1H), 5.20(d,1H), 5.35(s,1H), 6.50(s,1H), 7.21(s,2H) |

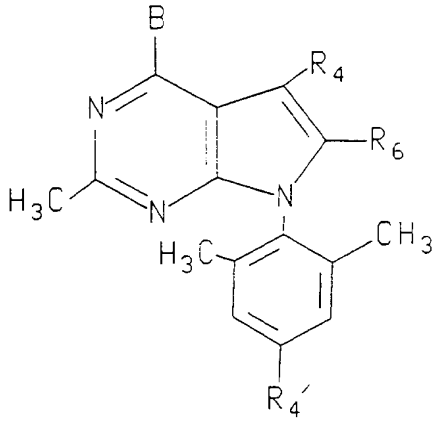
EXAMPLE 18

4-sec-Butoxy-1-(2,5,6-trimethylphenyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

Sodium hydride (0.114g, 4.77mmol, 60% in oil) was washed with hexane, then treated with 2-butanol (1.18g, 15.90 mmol). After 20 minutes, a mixture of 4-chloro-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine(0.500g,1.59mmol) in 5 ml of anhydrous tetrahydrofuran was added to the reaction mixture and stirred for 2 hours. The mixture was concentrated to dryness, dissolved in ethyl acetate and water. The organic layer was separated, washed with brine, dried, and concentrated to give a clear oil. The oil residue was purified through silica gel column chromatography using 20% ethyl acetate in hexane as eluent to give a clear oil which crystallized under high vacuo to give 0.450 g (80.5%) of an off-white solid. The solid was recrystallized from i-propanol to give gold crystals, mp 178-180°C.

EXAMPLE 19

The following compounds were prepared starting with the appropriate alcohol or thiol and 4-chloro-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine or 4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine and employing the general procedure of Example 18.




| B | $R_4'$ | $R_4$ | $R_6$ | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|---|
| $OCHEt_2$ | Me | Me | Me | 0.99(t,6H), 1.74(m,4H), 1.84(s,6H), 1.92(s,3H), 2.34(s,3H), 2.37(s,3H), 2.48(s,3H), 5.34(m,1H), 6.98(s,2H) |
| $OCHMe_2$ | Me | Me | Me | 1.41(d,6H), 1.82(s,6H), 1.91(s,3H), 2.33(s,3H), 2.36(s,3H), 2.48(s,3H), 5.55(m,1H), 6.98(s,2H) |
| OCH(Me)(Et) | Me | Me | Me | 1.02(t,3H), 1.28(d,3H), 1.65-1.80(m,2H), 1.83(s,6H), 1.92(s,3H), 2.33(s,3H), 2.37(s,3H), 2.48(s,3H), 5.38(m,1H), 6.98(s,2H) |
| OCH(Et)(n-Pr) | Me | Me | Me | 0.94(t,3H), 0.97(t,3H), 1.38-1.60(m,2H), 1.6-1.8(m,4H), 1.82(s,6H), 1.90(s,3H), 2.32(s,3H), 2.35(S,3H), 2.46(s,3H), 6.96(s,2H) |
| OCH(Et)(n-Bu) | Me | Me | Me | 0.90(t,3H), 0.99(t,3H), 1.3-1.5(m,4H), 1.6-1.8(m,4H), 1.832(s,3H), 1.837(s,3H), 1.92(s,3H), 2.34(s,3H), 2.36(s,3H), 2.48(s,3H), 5.39(m,1H), 6.98(s,2H) |

| B | $R_4'$ | $R_4$ | $R_6$ | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|---|---|---|
| OCH(Et)(n-pentyl) | Me | Me | Me | 0.88(t,3H), 0.98(t,3H), 1.4-1.6(m,6H), 1.6-1.8(m,4H), 1.82(s,6H), 1.90(s,3H), 2.32(s,3H), 2.36(s,3H), 2.47(s,3H), 5.40(m,1H), 6.96(s,2H) |
| OCH(Et)(n-hexyl) | Me | Me | Me | 0.85(t,3H), 0.97(t,3H), 1.20-1.50(m,8H), 1.6-1.8(m,4H), 1.82(s,6H), 1.90(s,3H), 2.32(s,3H), 2.35(s,3H), 2.46(s,3H), 5.37(m,1H), 6.96(s,2H) |
| $OCH(n\text{-}Pr)_3$ | Me | Me | Me | 0.94(t,3H), 1.4-1.6(m,4H), 1.6-1.8(m,4H), 1.83(s,6H), 1.91(s,3H), 2.33(s,3H), 2.36(S,3H), 2.48(s,3H), 5.50(m,1H), 6.97(s,2H) |
| $OCH(Et)(CH_2OMe)$ | Me | Me | Me | 1.03(t,3H), 1.82(s,3H), 1.83(s,3H), 1.91(s,3H), 2.33(s,3H), 2.37(s,3H), 2.47(s,3H), 3.43(s,3H), 3.68(m,2H), 5.55(m,1H), 6.97(s,2H) |
| $OCHEt_2$ | Me | Me | H | 0.99(t,6H), 1.63(m,4H), 1.92(s,6H), 2.32(s,3H), 2.41(s,3H), 2.50(s,3H), 5.35(m,1H), 6.52(s,1H), 6.96(s,2H) |
| $OCH(Et)(CH_2OMe)$ | Me | Me | H | 1.00(t,3H), 1.6-1.8(m,2H), 1.86(s,3H), 1.87(s,3H), 2.28(s,3H), 2.40(s,3H), 2.489s,3H), 3.40(s,3H), 3.62(m,2H), 5.51(m,1H), 6.48(s,1H), 6.92(s,2H) |
| $OCH_2$-(S)-$CH(NH_2)(Et)$ | Br | Me | H | 1.03(t,3H), 1.3-1.5(m,2H), 1.91(s,6H), 2.42(s,3H), 2.51(s,3H), 4.13(m,1H), 4.26(m,1H), 4.44(m,1H), 6.52(s,1H), 7.29(s,2H) |
| S-CH(Me)-CH(OH)(Me) | Br | Me | H | 1.25(d,3H), 1.41(d,3H), 1.87(s,3H), 1.89(s,3H), 2.50(s,3H), 2.55(s,3H), 4.1-4.3(m,2H), 6.63(s,1H), 6.65(brs,1H), 7.30(s,2H) |

EXAMPLE 20

A. 2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile

A mixture of 4-chloro-2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine (10.000 g, 31.90 mmol) and potassium cyanide (20.75 g, 319 mmol) in 100

ml dimethylsulfoxide was heated at 130°C oil bath over weekend. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give 9.61 g (99%) of brown soild. The solid was recrystallized from i-propanol to give 6.34 g (65%) of the title compound as light golden crystals, mp 188-190°C. $^1$H NMR ($CDCl_3$) $\delta$ 1.8(s,6H), 2.07(s,3H), 2.36(s,3H), 2.50(s,3H), 2.65(s,3H), 7.00(s,2H).

B. 2-Methyl-1-[2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-butan-1-one

To a solution of sec-butyl magnesium chloride (1.5 ml, 3.0 mmol, 2 M in diethyl ether) in 24 ml of dry tetrahydrofuran was added 2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile (0.814 g, 2.67 mmol) at room temperature and stirred for 5 hours. The mixture was quenched with 5 ml of 2N HCl, neutralized with saturated sodium bicarbonate, extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow solid. The solid was purified through silica gel column chromatography using chloroform as eluent to give 0.884 g (90%) of the title compound as yellow crystals, mp 133-135°C.

EXAMPLE 21

[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one and 1-[2,5,6-Trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pentan-1-one were prepared starting from 2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile, and ethyl magnesium chloride and n-BuLi. respectively, employing the general procedure of Example 20B.

EXAMPLE 22

[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-ol

A solution of 2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one (0.300 g, 0.89 mmol) in 10 ml of methanol was treated with sodium borohydride ($NaBH_4$) (0.169 g, 4.47 mmol) at room temperature and stirred for 15 minutes. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried, and concentrated to give 0.291 g (96%) of the title compound as light yellow crystals. The crystals were recrystallized from i-propanol to give light yellow crystals, mp 143-144°C.

EXAMPLE 23

The following compounds were prepared by reduction of the corresponding ketone derivative with $NaBH_4$ by the procedure described in the Example 22:

1-[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pentan1-ol; and

2-Methyl-1-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-butan-ol.

EXAMPLE 24

The following compounds were prepared by reaction of the corresponding alcohol derivative with NaH, followed by reacting with alkyl iodide using the procedure analogous to that described in Example 12:

4-(1-Methoxy-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;

4-(1-Ethoxy-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine; and

4-(1-Methoxy-2-methyl-butyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine.

EXAMPLE 25

[2,5,6-Trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pentan-3-ol

A solution of 1-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one (0.220 g, 0.656 mmol) in 10 ml of dry THF was treated with ethyl magnesium bromide (0.787 mmol, 0.39 ml, 2.0 m in THF) at 0°C and stirred at room temperature for 1 hour. The mixture was quenched with diluted HCl, neutralized with aqueous NaOH and extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow solid. The solid was redcrystallized from ethyl ether/ethyl acetate to give off-white crystals, mp 164-166.5°C.

EXAMPLE 26

[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-hexan-3-ol

The title compound was prepared by reacting 1-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one with n-propyl magnesium chloride using the procedure described in Example 25.

EXAMPLE 27

(1-Ethyl-1-fluoro-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

The title compound was prepared by reacting of 3-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pentan-3-ol with dimethylaminosulfur trifluoride using the procedure described in Example 11.

EXAMPLE 28

(1-Ethyl-propenyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of 3-[2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pentan-3-ol (0.041 g, 0.122 mmol), concentrated sulfuric acid (0.055 g, 0.56 mmol) and acetic acid (0.136 g, 2.27 mmol) was heated to reflux for 1 hour, cooled, diluted with water, basified to pH 10 with 2 N NaOH and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to dryness to give 43 mg of the title compound as a clear oil. The oil was purified through silica gel column chromatography to give 40 mg of the title compound as a white solid, mp 59-61°C.

EXAMPLE 29

Compounds listed in the following Table II in which B is CH(OAc)(CHMeEt) and a mixture of two isomers 4-(1-ethyl-butenyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine and 4-(1-n-propyl-propenyl)-2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine [see Table II in which B is C(=CHEt)(Et) and C(=CHMe)(n-Pr)] were prepared by a procedure analogous to that described in Example 28.

EXAMPLE 30

(1-Ethyl-butyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of two isomers, 4-(1-ethyl-butenyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine and 4-(1-n-propyl-propenyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine (67 mg, 0.185 mmol) in ethyl acetate (18 ml) and 10% Pd/C (38 mg) was hydrogenated at 50 psi for 15 hours. The mixture was filtered through celite. The filtrated was washed with brine, dried and concentrated to give 119 mg of oil. The oil was purified through silica gel column

chromatography using 7% ethyl acetate in hexane as eluent to give 31 mg (46%) of the title compound as off-white crystals, mp 100-102°C.

EXAMPLE 31

[-2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one oxime

A mixture of 1-[-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one (0.598 g, 1.783 mmol), hydroxylamino hydrochloride (0.370 g, 5.35 mmol), sodium acetate (0.439 g, 5.35 mmol) in MeOH (30 ml) was stirred at room temperature for 24 hours. The mixture was concentrated to dryness. The residue was diluted with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 0.657 g of a white glass form. The glass form was purified through silica gel column chromatography to separated both E (white crystals, mp 162-164°C, confirmed by X-ray structural analysis) and Z (white crystals, mp 84-87°C) isomers and a mixture of E and Z isomers (mp-150-190°C).

EXAMPLE 32

1-[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propylamine

Hydrogenation of 1-[-2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one oxime with 10% Pd/C in MeOH using the general procedure described in Example 28 resulted in the title compound.

EXAMPLE 33

[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylmethyl]-formamide

A mixture of 2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile (1.000 g, 3.29 mmol), 1:1 Al/Ni alloy (1.0 g) in 70% aqueous formic acid (10 ml) was stirred at room temperature for 1 hour. The mixture was filtered through Celite, washed with 100 ml of water and 100 ml of ethyl acetate. The organic layer was separated, dried and concentrated to give a light green oil. The oil was purified through silica gel column chromatography using 2% methanol in chloroform as eluent to give 0.960 g (86.5%) of the title compound as an off-white soild. The solid was recrystallized from ethyl acetate to give a light yellow crystals, mp 202-204°C.

EXAMPLE 34

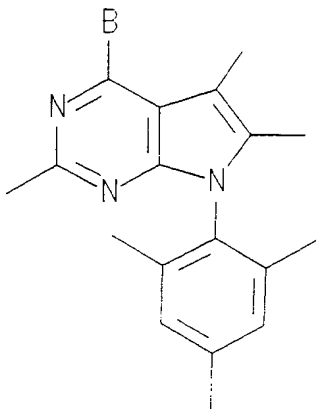
N-[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylmethyl]-acetamide

A mixture of 2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile (0.500 g, 1.64 mmol) and 10% Pd/C (0.500 g) in ethanol was hydrogenated at 55 psi for 5 hours. The mixture was filtered through celite and the filtrate was concentrated to give 0.500g (98.8%) of N-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylmethyl]-amine.

A mixture of N-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylmethyl]-amine (0.200 g, 0.648 mmol), acetic anhydride (0.132 g, 1.30 mmol), triethylamine (0.132 g, 1.30 mmol) in anhydrous methylene chloride (1 ml) was stirred at room temperature for 1 hour. The mixture was quenched with water and extracted with methylene chloride. The organic layer was separated, dried and concentrated to give 0.217 g (95.6%) of the title compound as a light tan solid. The solid was purified through silica gel column chromatography using 5% methanol in chloroform as eluent to give 0.200 g (88.1%) of the title compound as golden crystals, mp 140-143°C.

The $^1$H NMR data of the compounds which are described in the Examples 20 to 34 are listed in the following Table.

Table II



| B | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|
| CO-(n-Bu) | 1.00(t,3H), 1.4-1.6(m,2H), 1.7-1.9(m,2H), 1.83(s,6H), 2.06(s,3H), 2.34(s,3H), 2.35(s,3H), 2.38(s,3H), 3.27(t,2H), 7.03(s,2H) |
| COEt | 1.26(t,3H), 1.81(s,6H), 2.04(s,3H), 2.32(s,3H), 2.36(s,3H), 2.68(s,3H), 3.27(q,2H), 7.00(s,2H) |
| CO-CH(Me)(Et) | 0.99(t,3H), 1.24(d,3H), 1.45-1.65(m,1H), 1.7-1.9(m,1H), 1.83(s,6H), 2.05(s,3H), 2.30(s,3H), 2.37(s,3H), 2.68(s,3H), 3.91(m,1H0, 7.03(s,2H) |
| CH(OH)(n-Bu) | 0.95(t,3H), 1.2-1.8(m,6H), 1.77(s,3H), 1.87(s,3H), 2.00(s,3H), 2.37(s,3H), 2.39(s,3H), 2.63(s,3H), 5.20(dd,1H), 7.02(s,2H) |
| CH(OH)(Et) | 1.12(t,3H), 1.6-2.0(m,2H), 1.77(s,3H), 1.87(s,3H), 2.00(s,3H), 2.37(s,3H), 2.39(s,3H), 2.63(s,3H), 4.97(d,1H), 5.15(m,1H), 7.02(s,2H) |
| CH(OMe)(Et) | 1.02(t,3H), 1.82(s,3H), 1.83(s,3H), 2.01(s,3H), 1.8-2.1(m,2H), 2.36(s,3H), 2.45(s,3H), 2.669s,3H), 3.359s,3H0, 4.68(t,1H), 7.01(s,2H) |
| CH(OEt)(Et) | 1.02(t,3H), 1.22(t,3H), 1.82(s,3H), 1.83(s,3H), 1.7-2.1(m,2H), 2.36(s,3H), 2.46(s,3H), 2.65(s,3H), 3.49(m,2H), 4.75(t,1H), 7.01(s,2H) |
| CH(OMe)(CHMeEt) | 0.68(d,1.8H), 0.83(t,1.2H), 0.95(t,1.8H), 1.10(d,1.2H), 1.1-1.5(m,2H), 1.9-2.2(m,1H). 1.8(3 sets of s,6H), 2.0(s,3H), 2.359s,3H0. 2.53(s,3H0, 2.65(s,3H), 3.25(s,1.8H), 3.30(s,1.2H), 4.42(d,0.6H), 4.5(d,0.4H), 7.0(s,2H) |
| CH(OAc)(CHMeEt) | 0.7(d,1.5H), 0.85(t,1.5H), 0.94(t,1.5H), 1.1(d,1.5H), 1.1-1.5(m,2H), 1.81(s,1.5H), 1.83(s,3H), 1.869s,1.5H), 2.0(s,3H), 2.22(s,1.5H), 2.24(s,1.5H), 2.2-2.4(m,0.5H), 2.32(s,3H), 2.49(s,1.5H), 2.51(s,1.5H), 2.60(s,3H), 3.0-3.2(m,0.5H), 6.12(m,1H), 7.0(s,2H) |
| $CFEt_2$ | 0.90(t,6H), 1.83(s,6H), 2.03(s,3H), 2.0-2.4(m,4H), 2.38(s,6H), 2.59(s,3H), 7.02(s,2H) |
| $CEt_2(OH)$ | 071(t,6H), 1.79(s,6H), 2.02(s,3H), 2.0-2.4(m,4H), 2.36(s,3H), 2.47(s,3H), 2.61(s,3H), 7.01(s,2H) |

| B | $^1$H NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|
| C(Et)(n-Pr)(OH) | 0.71(t,3H), 0.84(t,3H), 1.4-1.6(m,2H), 1.80(s,3H), 1.81(s,3H), 2.04(s,3H), 1.9-2.2(m,4H), 2.38(s,3H), 2.49(s,3H), 2.63(s,3H), 6.83(s,1H), 7.03(s,2H) |
| CH(Et)(NH-n-Pr) | 0.87(t,3H), 0.90(t,3H), 1.5-1.7(m,2H), 1.80(s,3H), 1.83(s,3H), 2.00(s,3H), 1.9-2.2(m,2H), 2.36(s,3H), 2.41(s,3H), 2.42(s,3H), 2.3-2.5(m,1H), 2.7-2.9(m,1H), 4.48(m,1H), 7.019s,2H), 7.15(s,1H), |
| =NOH)(Et) | 1.0-1.2(m,3H), 1.79(s,1.5H), 1.80(s,1.5H), 1.99(s,1,.5H), 2.00(s,1.5H), 2.22(s,3H0, 2.35(s,3H), 2.65(s,1.5H), 2.68(s,1.5H), 2.7(q,1H), 2.99(q,1H), 6.93(s,2H), 9.05(brs,1H) |
| CH(Et)(NH2) | 1.04(t,3H), 1.79(s,3H), 1.85(s,3H), 1.7-2.0(m,2H), 1.99(s,3H), 2.36(s,3H), 2.42(s,3H), 2.62(s,3H), 4.52(m,1H), 7.01(s,2H) |
| =CHMe)(Et) | 1.00(t,2.1H), 1.1(t,0.9H), 1.47(d,0.9H), 1.82(s,6H), 1.9(d,2.1H), 2.02(s,3H), 2.25(s,3H), 2.4-2.8(m,5H), 5.6-5.8(m,1H), 7.0(s,2H) |
| =CHEt)(Et) + C(=CHMe)(n-Pr) | (m,5.4H), 1.82(s,6H), 1.869d,1.8H), 2.0(s,3H), 2.20(s,.1.2H), 2.21(s,1.8H), 2.359s,3H), 2.60(s,1.8H), 2.61(s,1.2H), 2.3-2.8(m,2.8H),5.4-5.8(m,1H), 6.959s,2H) |
| CH(n-Bu)(Et) | 0.83(t,3H), 0.88(t,3H), 1.1-1.49(m,2H), 1.6-2.2(m,4H), 1.82(s,3H), 1.83(s,3H), 1.98(s,3H), 2.35(s,3H), 2.43(s,3H), 2.61(s,3H), 3.33(m,1H), 7.00(s,2H) |
| CH2NHCHO | 1.79(s,6H), 2.00(s,3H), 2.35(s,3H), 2.48(s,3H), 2.62(s,3H), 4.98(d,2H), 7.01(s,2H), 8.05(brs,1H), 8.38(s,1H) |
| CH2NHCOCH3 | 1.79(s,6H), 1.97(s,3H), 2.12(s,3H), 2.34(s,3H), 2.43(s,3H), 2.61(s,3H), 4.90(d,2H), 6.99(s,2H), 7.46(brs,1H) |

Example 35

A. 1-[2-Amino-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-3-yl]-2-ethyl-butan-1-one

A mixture of 3-hydroxy-2-butanone (0.637 g, 7.23 mmol), 2,4,6-trimethylaniline (0.973 g, 0.719 mmol) and p-toluene sulfonic acid (0.012 g ) in 15 ml of benzene was heated at reflux under Dean-Stark trap for 3 hours. A solution of $(Et)_2CHCOCH_2CN$ (1.008 g, 7.24 mmol) was added to the reaction mixture and heated at reflux overnight. The mixture was cooled and diluted with ethyl acetate and water. The organic layer was separated and washed with water, aqueous sodium carbonate, and then brine; dried and concentrated to give a brown oil which contains the desired compound. 0.368 g of the desired compound was isolated after silica gel column chromatography using chloroform as eluent. $^1H$ NMR ($CDCl_3$) $\delta$ 0.94 (t,6H), 1.5-1.8 (m,4H), 1.73 (s,3H), 1.98 (s,6H), 2.26 (s,3H), 2.34 (s,3H), 3.00 (m,1H), 5.78 (brs,2H), 6.99 (s,2H) ppm.

B. N-[3-(2-Ethyl-butyryl)-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-2-yl]-acetamide

A mixture of the title compound from Example 35A (0.326 g, 1 mmol) and acetic anhydride (0.108 g, 1.05 mmol) in acetic acid (3 ml) was heated at reflux for 2 hours. The mixture was concentrated to dryness, diluted with water and extracted with ethyl acetate. The organic layer was washed with aqueous sodium carbonate and brine, dried and concentrated to give a dark oil. The oil was purified by silica gel column chromatography to give 107 mg of the title compound as a brown oil. $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (t,6H), 1.6-1.8 (m,4H), 1.76 (s,3H), 1.88 (s,3H), 1.93 (s,6H), 2.25 (s,3H), 2.28 (s,3H), 2.90-3.00 (m,1H), 6.89 (s,2H) ppm.

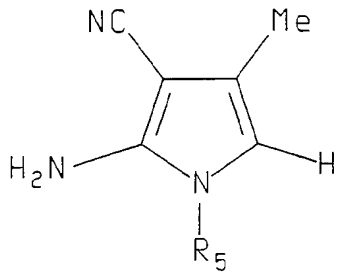
C. 4-(1-Ethylpropyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of the title compound of Example 35B (100 mg, 0.27 mmol) and ammonium chloride in 1.6 g of acetamide was heated at reflux for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give the desired product which was purified by silica gel column chromatography to give the title compound as a yellow oil. $^1H$ NMR ($CDCl_3$) $\delta$ 0.85 (t,6H), 1.7-2.0 (m,4H), 1.83 (s,6H), 1.99 (s,3H), 2.35 (s,3H), 2.44 (s,3H), 2.61 (s,3H), 3.25-3.35 (m,1H), 7.00 (s,2H) ppm.

The following Preparations illustrate the synthesis of intermediates.

Preparation 1

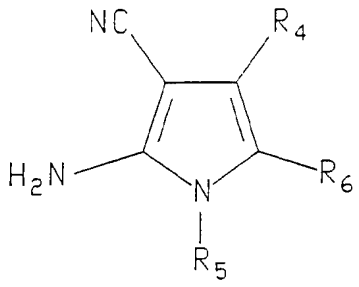
The following compounds were prepared starting from the appropriate aniline and employing the general procedure of Example 1A.




| $R_5$ | $^1$H-NMR($CDCl_3$) $\delta$ (ppm) |
|---|---|
| 3,5-ditrifluoromethylphenyl | 2.2(s,3H), 4.0(s,2H), 6.15(s,1H), 7.9(s,2H) |
| 2,5-dimethylphenyl | 2.04(s,3H), 2.12(s,3H), 2.35(s,3H), 3.85(s,2H), 5.90(s,1H), 7.0(s,1H), 7.10-7.25(m,2H) |
| 2-methyl-4-iodophenyl | 2.05(s,3H), 2.10(s,3H), 3.80(s,2H), 5.85(s,1H), 6.92(d,1H), 7.60(dd,1H), 7.70(d,1H) |
| 3-methyl-4-chlorophenyl | 2.10(s,3H), 2.40(s,3H), 4.03(s,2H), 6.03(s,1H), 7.10(dd,1H), 7.21(d,1H), 7.45(d,1H) |
| 4-bromo-2,6-dimethylphenyl | 2.01(s,6H), 2.10(s,3H), 3.70(brs,2H), 5.72(s,1H), 7.30(s,2H) |
| 2-bromo-4,6-dimethylphenyl | 2.06(s,3H), 2.13(s,3H), 2.35(s,3H), 3.83(brs,2H), 5.81(s,1H), 7.08(s,1H), 7.35(s,3H) |
| 4-chloro-2,6-dimethylphenyl | 2.01(s,6H), 2.10(s,3H), 3.75(brs,2H), 5.75(s,1H), 7.14(s,2H) |

Preparation 2

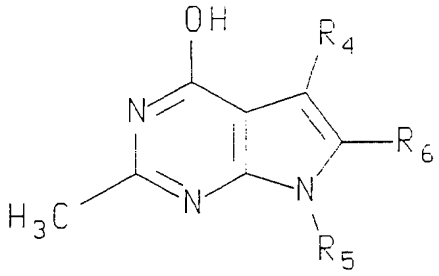
The following compounds were prepared starting from 3-hydroxy-2-butanone or 4-hydroxy-3-hexanone and the appropriate aniline and employing the general procedure of Example 2A.



| $R_4$ and $R_6$ | $R_5$ | $^1$H-NMR($CDCl_3$) $\delta$ (ppm) |
|---|---|---|
| Me | 2,4-dimethylphenyl | 1.70(s,3H), 1.95(s,3H), 2.05(s,3H), 2.38(s,3H), 3.7(s,2H), 6.95-7.20(m,3H) |
| Me | 2,6-dimethylphenyl | 1.67(s,3H), 1.98(s,6H), 2.05(s,3H), 2.90(brs,2H), 7.05-7.21(m,3H) |
| Et | 2,4,6-trimethylphenyl | No purification, the material was used directly for the next reaction step |

Preparation 3

The following compounds were prepared starting from the corresponding compounds of preparations 1 and 2 and employing the general procedures of Examples 1B and 1C.

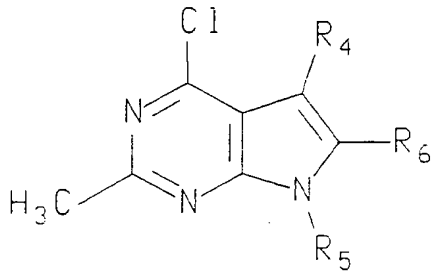


| $R_4$=Me, $R_6$=H | $^1$H-NMR (solvent) $\delta$ (ppm) |
|---|---|
| $R_5$=3,5-ditrifluoromethylphenyl | (DMSO-d6) 2.32(s,3H), 7.50(s,1H), 8.05(s,1H), 8.55(s,1H), 12.10(s,1H) |
| $R_5$=2,5-dimethylphenyl | ($CDCl_3$) 2.04(s,3H), 2.35(s,3H), 2.467(s,3H), 2.470(s,3H), 6.57(s,1H), 7.0-7.3(m,3H), 12.08(s,3H) |

| | |
|---|---|
| $R_5$=3-methyl-4-chlorophenyl | (DMSO-$d_6$) 2.29(s,3H), 2.31(s.3H), 2.38(s,3H), 7.12(s,1H), 7.55(m.2H), 7.67(d,1H), 11.90(s,1H) |
| $R_5$=4-bromo-2,6-dimethylphenyl | ($CDCl_3$) 1.94(s,6H), 2.40(s,3H), 2.45(s,3H), 6.39(s,1H), 7.29(s,2H) |
| $R_5$=2-bromo-4,6-dimethylphenyl | (DMSO-$d_6$) 1.91(s,3H), 2.20(s.3H), 2.32(s,3H), 2.34(s,3H), 6.68(s,1H), 7.21(s,1H), 7.44(s,1H),11.80(s,1H) |
| $R_5$ = 4-chloro-2,6-dimethylphenyl | ($CDCl_3$) 1.91(s,6H), 2.38(s,3H), 2.40(s,3H), 6.34(s,1H), 7.08(s.2H) |
| $R_4$ & $R_6$ = Me | $^1$H-NMR (solvent) $\delta$ (ppm) |
| $R_5$=2,4,6-trimethylphenyl | ($CDCl_3$) 1.85(s,6H), 1.87(s,3H), 2.34(s,3H), 2.41(s,3H), 2.44(s.3H), 7.00(s,2H), 12.2(s,1H) |
| $R_5$=2,4-dimethylphenyl | ($CDCl_3$) 1.90(s,3H), 1.93(s,3H), 2.38(s,3H), 2.42(s,6H), 7.0-7.2(m,3H), 12.25(s,1H) |
| $R_5$=2,6-dimethylphenyl | ($CDCl_3$) 1.80-1.90(m,9H), 2.39(s,3H), 2.49(s,3H), 7.04-7.20(m,3H), 12.2(s,1H) |

Preparation 4

The following compounds were prepared starting from the corresponding compounds of Preparation 3 and employing the general procedure in Example 1D.

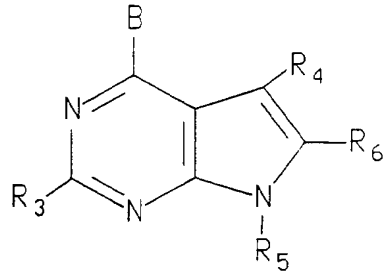



| $R_4$=Me, $R_6$=H | $^1$H-NMR ($CDCl_3$) $\delta$ (ppm) |
|---|---|
| $R_5$=3,5-ditrifluoromethylphenyl | 2.53(s,3H), 2.74(s,3H), 7.27(s.1H), 7.82(s,1H), 8.29(s,2H) |

| | |
|---|---|
| $R_5$=2,5-dimethylphenyl | 2.01(s,3H), 2.35(s,3H), 2.50(s,3H), 2.66(s,3H), 6.91(s,1H), 7.05(s,1H), 7.10-7.30(m2H) |
| $R_5$=3-methyl-4-chlorophenyl | 2.46(s,3H), 2.51(s,3H), 2.74(s,3H), 7.15(s,1H), 7.47(s,2H), 7.55(s,1H) |
| $R_5$=4-bromo-2,6-dimethylphenyl | 1.89(s,6H), 2.49(s,3H), 2.62(s,3H), 6.75(s,1H), 7.32(s,2H) |
| $R_5$ = 2-bromo-4,6-dimethylphenyl | 1.96(s,3H), 2.37(s,3H), 2.52(s,3H), 2.65(s,3H), 6.82(s,1H), 7.11(s,1H), 7.38(s,1H) |
| $R_4$ and $R_6$ = Me | $^1$H-NMR ($CDCl_3$) $\delta$ (ppm) |
| $R_5$=2,4,6-trimethylphenyl | 1.81(s,6H), 1.99(s,3H), 2.35(s,3H), 2.46(s,3H), 2.59(s,3H), 7.01(s,2H) |
| $R_5$=2,4-dimethylphenyl | 1.84(s,3H), 2.03(s,3H), 2.39(s,3H), 2.44(s,3H), 2.59(s,3H), 6.90-7.15(m,3H) |
| $R_5$=2,6-dimethylphenyl | 1.83(s,6H), 1.98(s,3H), 2.45(s,3H), 2.58(s,3H), 7.10-7.30(m,3H) |
| $R_5$=4-chloro-2,6-dimethylphenyl | 1.91(s,6H), 2.51(s,3H), 2.64(s,3H), 6.77(s,1H), 7.17(s,2H) |
| $R_4$ and $R_6$ = Et | $^1$H-NMR ($CDCl_3$) $\delta$ (ppm) |
| $R_5$=2,4,6-trimethylphenyl | 0.96(t,3H), 1.31(t,3H), 1.85(s,6H), 2.38(s,6H), 2.46(q,2H), 2.62(s,3H), 2.92(q,2H), 7.02(s,2H) |

## CLAIMS

1. A compound of the formula



I

and the pharmaceutically acceptable acid addition salts thereof, wherein

B is $NR_1R_2$, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$;

$R_1$ is hydrogen, or $C_1$-$C_6$ alkyl which may be substituted by one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $C_1$-$C_8$ alkoxy, O-C -($C_1$-$C_6$ alkyl), O-C NH($C_1$-$C_4$ alkyl), O-C -N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), amino, NH($C_1$-$C_4$ alkyl), N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), S($C_1$-$C_6$ alkyl), N($C_1$-$C_4$alkyl)C ($C_1$-$C_4$ alkyl), NHC ($C_1$-$C_4$ alkyl), COOH, C O($C_1$-$C_4$ alkyl), C NH($C_1$-$C_4$ alkyl), C N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), SH, CN, $NO_2$, SO($C_1$-$C_4$ alkyl), $SO_2$($C_1$-$C_4$ alkyl), $SO_2NH$($C_1$-$C_4$ alkyl), $SO_2N$($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), and said $C_1$-$C_6$ alkyl may contain one or two double or triple bonds;

$R_2$ is $C_1$-$C_{12}$ alkyl, aryl or ($C_1$-$C_{10}$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or ($C_1$-$C_6$ alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, benzyl or $C_1$-$C_4$ alkanoyl, wherein $R_2$ may be substituted independently by from one to three of chloro, fluoro, or $C_1$-$C_4$ alkyl, or one of hydroxy, bromo, iodo, C-

$C_6$ alkoxy, O-C(=O)-($C_1$-$C_6$ alkyl), O-C(=O)-N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), S($C_1$-$C_6$ alkyl), $NH_2$, $NH(C_1$-$C_2$ alkyl), $N(C_1$-$C_2$ alkyl) ($C_1$-$C_4$ alkyl), $N(C_1$-$C_4$ alkyl)-C(=O)($C_1$-$C_4$ alkyl), NHC(=O)($C_1$-$C_4$ alkyl), COOH, C(=O)O($C_1$-$C_4$ alkyl), C(=O)NH($C_1$-$C_4$ alkyl), C(=O)N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), SH, CN, $NO_2$, SO($C_1$-$C_4$ alkyl), $SO_2$($C_1$-$C_4$ alkyl), $SO_2NH$($C_1$-$C_4$ alkyl), $SO_2N$($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), and wherein said $C_1$-$C_{12}$ alkyl or $C_1$-$C_{10}$ alkylene may contain one to three double or triple bonds; or

$NR_1R_2$ or $CR_1R_2R_{11}$ may form a saturated 3- to 8-membered carbocyclic ring of which the 5- to 8-membered ring may contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, benzyl or $C_1$-$C_4$ alkanoyl;

$R_3$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O($C_1$-$C_6$ alkyl), NH($C_1$-$C_6$ alkyl), N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), SH, S($C_1$-$C_4$ alkyl), SO($C_1$-$C_4$ alkyl), or $SO_2$($C_1$-$C_4$ alkyl), wherein said $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl may contain one double or triple bond and may be substituted by from 1 to 3 substituents $R_5$ independently selected from the group consisting of hydroxy, $C_1$-$C_3$ alkoxy, fluoro, chloro or $C_1$-$C_3$ thioalkyl;

$R_4$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, amino, NH($C_1$-$C_6$ alkyl), N($C_1$-$C_6$ alkyl)($C_1$-$C_2$ alkyl), $SO_n$($C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said $C_1$-$C_6$ alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, NHC(=O)($C_1$-$C_4$ alkyl), NH($C_1$-$C_4$ alkyl), N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), C(=O)O($C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

$R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl,

piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, $NH(C_1$-$C_4$ alkyl), $N(C_1$-$C_4)(C_1$-$C_2$ alkyl), $COO(C_1$-$C_4$ alkyl), $CO(C_1$-$C_4$ alkyl), $SO_2NH(C_1$-$C_4$ alkyl), $SO_2N(C_1$-$C_4$ alkyl)$(C_1$-$C_2$ alkyl), $SO_2NH_2$, $NHSO_2(C_1$-$C_4$ alkyl), $S(C_1$-$C_6$ alkyl), $SO_2(C_1$-$C_6$ alkyl), wherein said $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl may be substituted by one or two of fluoro, chloro, hydroxy, $C_1$-$C_4$ alkoxy, amino, methylamino, dimethylamino or acetyl wherein said $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl may contain one double or triple bond; with the proviso that $R_5$ is not unsubstituted phenyl;

$R_6$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, formyl, amino, $NH(C_1$-$C_6$ alkyl), $N(C_1$-$C_6$ alkyl$)(C_1$-$C_2$ alkyl), $SO_n(C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said $C_1$-$C_6$ alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, $NHC(=O)(C_1$-$C_4$ alkyl), $NH(C_1$-$C_4$ alkyl), $N(C_1$-$C_4$ alkyl$)(C_1$-$C_2$ alkyl), $C(=O)O(C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

$R_{11}$ is hydrogen, hydroxy, fluoro, chloro, $COO(C_1$-$C_2$ alkyl), cyano, or $CO(C_1$-$C_2$ alkyl); and

$R_{12}$ is hydrogen or $C_1$-$C_4$ alkyl; with the proviso that (1) B is not straight chain $C_1$-$C_{12}$ alkyl, (2) when $R_5$ is unsubstituted cycloakyl, $R_3$ and $R_4$ are hydrogen, and $R_6$ is hydrogen or methyl, then B is not $NHR_2$ wherein $R_2$ is benzyl or thienylmethyl, and (3) when $R_5$ is p-bromophenyl, and $R_3$, $R_4$ and $R_6$ are methyl, then B not methylamino or hydroxyethylamino.

2. A compound according to claim 1 wherein B is $NR_1R_2$, $NHCHR_1R_2$, or $OCHR_1R_2$, wherein $R_1$ is $C_1$-$C_6$ alkyl, which may be substituted by one of hydroxy, fluoro or $C_1$-$C_2$ alkoxy, and may contain one double or triple bond, and $R_2$ is benzyl or $C_1$-$C_6$ alkyl which may contain one double or triple bond, wherein said $C_1$-$C_6$ alkyl or the phenyl in said benzyl may be substituted by fluoro, $C_1$-$C_6$ alkyl, or $C_1$-$C_6$ alkoxy

3. A compound according to claim 1 wherein B is $CR_1R_2R_{11}$, wherein $R_1$ is $C_1$-$C_6$ alkyl which may be substituted by one $C_1$-$C_6$ alkoxy or hydroxy, $R_2$ is benzyl or $C_1$-$C_6$ alkyl wherein said $C_1$-$C_6$ alkyl or the phenyl in said benzyl may be substituted by one $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, fluoro, chloro or bromo, and $R_{11}$ is hydrogen or fluoro.

4. A compound according to claim 1 wherein B is as defined in claim 1 and $R_2$ is $C_1$-$C_6$ alkyl which may be substituted by fluoro, $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkoxy and may contain one double or triple bond.

5. A compound according to claim 1 wherein B is as defined in claim 1 and $R_2$ is benzyl or methylthienyl, the phenyl or thienyl of which may be substituted by fluoro, chloro, $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkoxy.

6. A compound according to any one of claims 1 to 5 wherein $R_3$ is methyl, ethyl, fluoro, chloro, or methoxy.

7. A compound according to any one of claims 1 to 6 wherein $R_4$ and $R_6$ are hydrogen, methyl or ethyl.

8. A compound according to any one of claims 1 to 7 wherein $R_5$ is phenyl substituted by two or three substituents.

9. A compound according to claim 8 wherein said substituent is independently fluoro, chloro, bromo, iodo, $C_1$-$C_4$ alkoxy, trifluoromethyl, $C_1$-$C_6$ alkyl which may be substituted by one of hydroxy, $C_1$-$C_4$ alkoxy or fluoro and may have one double or triple bond, -($C_1$-$C_4$ alkylene)O($C_1$-$C_2$ alkyl), $C_1$-$C_3$ hydroxyalkyl, hydroxy, formyl, COO($C_1$-$C_2$ alkyl), -($C_1$-$C_2$ alkylene)amino, or -C(O)($C_1$-$C_4$ alkyl).

10. A compound according to claim 1 wherein said compound is

n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;

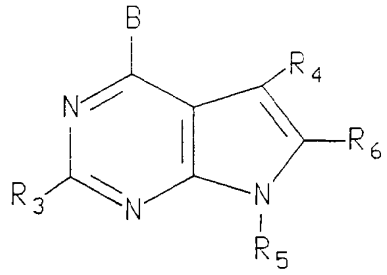
4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;

n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine; or

2-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol.

11. A pharmaceutical composition for the treatment of (a) illnesses induced or facilitated by corticotropin releasing factor or (b) inflammatory disorders such as arthritis, asthma and allergies; anxiety; depression; fatigue syndrome; headache; pain; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurogenerative diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; and fertility problems, which comprises a compound of the formula




I

and the pharmaceutically acceptable acid addition salts thereof, wherein

B is $NR_1R_2$, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$;

$R_1$ is hydrogen, or $C_1$-$C_6$ alkyl which may be substituted by one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $C_1$-$C_8$ alkoxy, O-C -($C_1$-$C_6$ alkyl), O-C NH($C_1$-$C_4$ alkyl), O-C -N($C_1$-$C_4$

O O O

alkyl)($C_1$-$C_2$ alkyl), amino, NH($C_1$-$C_4$ alkyl), N($C_1$-$C_2$ alkyl)($C_1$-$C_4$ alkyl), S($C_1$-$C_6$ alkyl), N($C_1$-$C_4$alkyl)C ($C_1$-$C_4$ alkyl), NHC ($C_1$-$C_4$ alkyl), COOH, C O($C_1$-$C_4$ alkyl), C NH($C_1$-$C_4$ alkyl), C N($C_1$-$C_4$ alkyl), SH, CN, $NO_2$, SO($C_1$-$C_4$ alkyl), $SO_2$($C_1$-$C_4$ alkyl), $SO_2NH$($C_1$-$C_4$ alkyl), $SO_2N$($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), and said $C_1$-$C_6$ alkyl may contain one or two double or triple bonds;

$R_2$ is $C_1$-$C_{12}$ alkyl, aryl or ($C_1$-$C_{10}$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or ($C_1$-$C_6$ alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, benzyl or $C_1$-$C_4$ alkanoyl, wherein $R_2$ may be substituted independently by from one to three of chloro, fluoro, or $C_1$-$C_4$ alkyl, or one of hydroxy, bromo, iodo, $C_1$-$C_6$ alkoxy, O-C -($C_1$-$C_6$ alkyl), O-C -N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), S($C_1$-$C_6$ alkyl), $NH_2$, NH($C_1$-$C_2$ alkyl), N($C_1$-$C_2$ alkyl) ($C_1$-$C_4$ alkyl), N($C_1$-$C_4$ alkyl)-C ($C_1$-$C_4$ alkyl), NHC ($C_1$-$C_4$ alkyl), COOH, C O($C_1$-$C_4$ alkyl), C NH($C_1$-$C_4$ alkyl), C N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), SH, CN, $NO_2$, SO($C_1$-$C_4$ alkyl), $SO_2$($C_1$-$C_4$ alkyl), $SO_2NH$($C_1$-$C_4$ alkyl), $SO_2N$($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), and wherein said $C_1$-$C_{12}$ alkyl or $C_1$-$C_{10}$ alkylene may contain one to three double or triple bonds; or

$NR_1R_2$ or $CR_1R_2R_{11}$ may form a saturated 3- to 8-membered carbocyclic ring, the 5- to 8-membered rings of which may contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, benzyl or $C_1$-$C_4$ alkanoyl;

$R_3$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O($C_1$-$C_6$ alkyl), NH($C_1$-$C_6$ alkyl), N($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), SH, S($C_1$-$C_4$ alkyl), SO($C_1$-$C_4$ alkyl), or $SO_2$($C_1$-$C_4$ alkyl), wherein said $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl may contain one

double or triple bond and may be substituted by from 1 to 3 substituents $R_6$ independently selected from the group consisting of hydroxy, $C_1$-$C_3$ alkoxy, fluoro, chloro or $C_1$-$C_3$ thioalkyl;

$R_4$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, formyl, $NH(C_1$-$C_6$ alkyl), $N(C_1$-$C_6$ alkyl)$(C_1$-$C_2$ alkyl), $SO_n(C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said $C_1$-$C_6$ alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, NHC($C_1$-$C_4$ alkyl), $NH(C_1$-$C_4$ alkyl), $N(C_1$-$C_4$ alkyl)$(C_1$-$C_2$ alkyl), C O($C_1$-$C_4$ alkyl), $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

$R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, $NH(C_1$-$C_4$ alkyl), $N(C_1$-$C_4)(C_1$-$C_2$ alkyl), $COO(C_1$-$C_4$ alkyl), $CO(C_1$-$C_4$ alkyl), $SO_2NH(C_1$-$C_4$ alkyl), $SO_2N(C_1$-$C_4$ alkyl)$(C_1$-$C_2$ alkyl), $SO_2NH_2$, $NHSO_2(C_1$-$C_4$ alkyl), $S(C_1$-$C_6$ alkyl), $SO_2(C_1$-$C_6$ alkyl), wherein said $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl may be substituted by one or two of fluoro, chloro, hydroxy, $C_1$-$C_4$ alkoxy, amino, methylamino, dimethylamino or acetyl wherein said $C_1$-$C_4$ alkyl and said $C_1$-$C_6$ alkyl may contain one double or triple bond; with the proviso that $R_5$ is not unsubtituted phenyl;

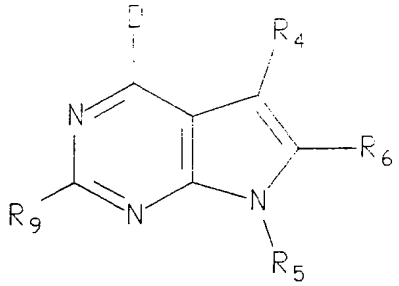
$R_6$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, formyl, amino, $NH(C_1$-$C_6$ alkyl), $N(C_1$-$C_6$ alkyl)$(C_1$-$C_2$ alkyl), $SO_n(C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said $C_1$-$C_6$ alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, NHC($C_1$-$C_4$ alkyl), $NH(C_1$-$C_4$ alkyl).

$N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $C(=O)O(C_1\text{-}C_4$ alkyl), $C_1\text{-}C_3$ alkoxy, $C_1\text{-}C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

$R_{11}$ is hydrogen, hydroxy, fluoro, chloro, $COO(C_1\text{-}C_2$ alkyl), cyano, or $CO(C_1\text{-}C_2$ alkyl); and

$R_{12}$ is hydrogen or $C_1\text{-}C_4$ alkyl, in an amount effective in the treatment of said illnesses, and a pharmaceutically acceptable carrier.

12. A compound of the formula



II

wherein

D is hydroxy, chloro, or cyano;

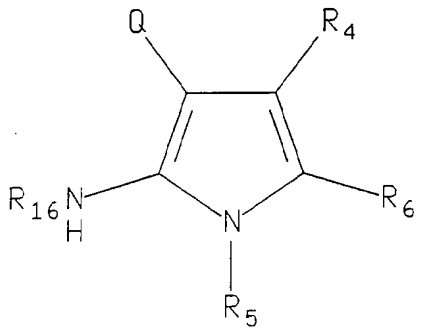
$R_4$ and $R_6$ are each independently hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1\text{-}C_6$ alkoxy, $SO_n(C_1\text{-}C_6$ alkyl), wherein n is 0, 1 or 2, or cyano, wherein said $C_1\text{-}C_6$ alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, $NHC(O)(C_1\text{-}C_4$ alkyl), $NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $C(O)O(C_1\text{-}C_4$ alkyl), $C_1\text{-}C_3$ alkoxy, $C_1\text{-}C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

$R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperdinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ alkanoyl, phenyl or benzyl, wherein each of the above groups may be substituted independently by from one to three of fluoro, chloro, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy or trifluoromethyl, or one of hydroxy, bromo, iodo, cyano, nitro, amino, $NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_4)(C_1\text{-}C_2$ alkyl), $COO(C_1\text{-}C_4$ alkyl), $CO(C_1\text{-}C_4$ alkyl),

$SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $SO_2NH_2$, $NHSO_2(C_1\text{-}C_4)$, $S(C_1\text{-}C_6$ alkyl), $SO_2(C_1\text{-}C_6$ alkyl), wherein said $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_6$ alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that $R_5$ is not unsubstituted phenyl; and

$R_9$ is hydrogen, $C_1\text{-}C_6$ alkyl or chloro; with the proviso that when (a) $R_4$ and $R_6$ are methyl, $R_9$ is hydrogen and D is hydroxy, then $R_5$ is not phenyl (1) substituted by one of halogen, nitro, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, or trifluoromethyl, and optionally in addition substituted by one or two of halogen, $C_1\text{-}C_6$ alkyl or $C_1\text{-}C_6$ alkoxy, or (2) di-or trisubstituted by one of nitro or trifluoromethyl and one or two of halogen, $C_1\text{-}C_6$ alkyl or $C_1\text{-}C_6$ alkoxy, and (b) when D is chloro, $R_4$ and $R_9$ are hydrogen, and $R_6$ is $C_1\text{-}C_6$ alkyl, then $R_5$ is not unsubstituted cyclohexyl.

13. A compound of the formula




VII

wherein

Q is $C(O)CHR_1R_2$ or cyano;

$R_1$ is hydrogen, or $C_1\text{-}C_6$ alkyl which may be substituted by one or two substituents $R_7$ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $C_1\text{-}C_8$ alkoxy, or nitro, and said $C_1\text{-}C_6$ alkyl may contain one or two double or triple bonds;

$R_2$ is $C_1\text{-}C_{12}$ alkyl, aryl or ($C_1\text{-}C_{10}$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or ($C_1\text{-}C_6$ alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, benzyl or $C_1\text{-}C_4$ alkanoyl, wherein $R_2$ may be substituted independently by

from one to three of chloro, fluoro, or $C_1$-$C_4$ alkyl, or one of hydroxy, bromo, iodo, $C_1$-$C_6$ alkoxy, nitro, SO($C_1$-$C_4$ alkyl), $SO_2$($C_1$-$C_4$ alkyl), $SO_2NH$($C_1$-$C_4$ alkyl), $SO_2N$($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), and wherein said $C_1$-$C_{12}$ alkyl or $C_1$-$C_{10}$ alkylene may contain one to three double or triple bonds;

$R_4$ and $R_6$ are each independently hydrogen, $C_1$-$C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1$-$C_6$ alkoxy, amino, or $SO_n$($C_1$-$C_6$ alkyl), wherein n is 0, 1 or 2, or cyano, wherein said $C_1$-$C_6$ alkyl may be substituted by one $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

$R_5$ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two O, S or N-Z wherein Z is hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkanoyl, phenyl or benzyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy or trifluoromethyl, or one of hydroxy, bromo, iodo, cyano, nitro, amino, NH($C_1$-$C_4$ alkyl), N($C_1$-$C_4$)($C_1$-$C_2$ alkyl), COO($C_1$-$C_4$ alkyl), CO($C_1$-$C_4$ alkyl), $SO_2NH$($C_1$-$C_4$ alkyl), $SO_2N$($C_1$-$C_4$ alkyl)($C_1$-$C_2$ alkyl), $SO_2NH_2$, $NHSO_2$($C_1$-$C_4$ alkyl), S($C_1$-$C_6$ alkyl), $SO_2$($C_1$-$C_6$ alkyl), wherein said $C_1$-$C_4$ alkyl and $C_1$-$C_6$ alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that $R_5$ is not unsubstituted phenyl; and

$R_{16}$ is hydrogen or C(O)$C_1$-$C_6$ alkyl; with the proviso that when Q is cyano, $R_4$ and $R_6$ are not both methyl.

# INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 93/10715

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D487/04 A61K31/505 C07D207/34 //(C07D487/04,239:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | DE,A,31 45 287 (TROPONWERKE) 19 May 1983 cited in the application see page 4, line 1 - line 5; claim 1 --- | 1,11 |
| X | EP,A,0 475 411 (MARION MERRELL DOW) 18 March 1992 see claim 1 ----- | 12 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 9 March 1994 | 23. 03. 94 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016 | Alfaro Faus, I |

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 93/10715

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| DE-A-3145287 | 19-05-83 | NONE | | |
| EP-A-0475411 | 18-03-92 | AU-A- | 8372991 | 19-03-92 |
| | | CA-A- | 2051012 | 15-03-92 |
| | | CN-A- | 1059909 | 01-04-92 |
| | | JP-A- | 4270282 | 25-09-92 |
| | | NZ-A- | 239750 | 25-02-94 |
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*A61K 38/22* (2006.01) *C07D 487/04* (2006.01)
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(74) Agent: **LAMIQUIZ, Jiarong L.**; WILSON SONSINI, 650 Page Mill Road, Palo Alto, California 94304 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: METHODS OF TREATING CONGENITAL ADRENAL HYPERPLASIA

(57) Abstract: Patients with congenital adrenal hyperplasia (CAH) need adequate care and treatment in order to lead normal lives. Hence, there is a need for new methods of treating CAH. This disclosure provides new compounds, salts, compositions and uses thereof in the treatment of CAH.

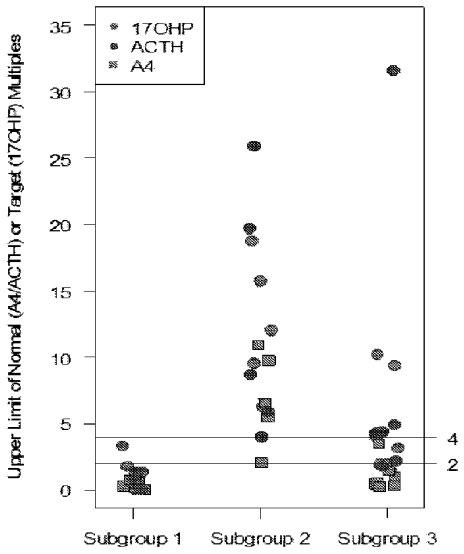



*FIG. 1*

WO 2021/016208 A1

[Continued on next page]

**Declarations under Rule 4.17:**

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

**Published:**

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

# METHODS OF TREATING CONGENITAL ADRENAL HYPERPLASIA

## CROSS-REFERENCE

**[0001]** This application claims priority to U.S. Provisional Patent Application No 62/876,176, filed July 19, 2019, and U.S. Provisional Patent Application No 63/047,822, filed on July 2, 2020, each of which is entirely incorporated herein by reference.

## BACKGROUND

**[0002]** Congenital adrenal hyperplasia (CAH) is a group of rare inherited autosomal recessive disorders characterized by a deficiency of one of the enzymes needed to make specific hormones. CAH affects the adrenal glands located at the top of each kidney. Normally, the adrenal glands are responsible for producing three different hormones: 1) glucocorticoids, which gauge the body's response to stress, illness, or injury; 2) mineralocorticoids, which regulate salt and water levels; and 3) androgens, which are male sex hormones. An enzyme deficiency may make the body unable to produce one or more of these hormones, which in turn may result in the overproduction of another type of hormone precursor in order to compensate for the loss.

## SUMMARY

**[0003]** Congenital Adrenal Hyperplasia (CAH) patients need adequate care and treatment in order to lead normal lives. Hence, there is a need for new methods of treating CAH. This disclosure provides new compounds, salts, compositions and uses thereof in the treatment of CAH.

**[0004]** In an aspect, the present disclosure provides methods for treating Congenital Adrenal Hyperplasia (CAH). The method comprises administering a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof to a subject, wherein when said subject has a level of at least one steroid hormone that is less than two times an upper limit of a reference range of said at least one steroid hormone level , a dose of said steroid or a pharmaceutically acceptable salt thereof is reduced compared to a dose of said steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient that does not receive said $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof.

**[0005]** In some embodiments, the subject has a level of a second and different steroid hormone that is less than two times an upper limit of a reference range of said second and different steroid hormone level. In some embodiments, the steroid hormone is selected from the group consisting of adrenocorticotropic hormone (ACTH), androstenedione (A4), 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone,

aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, dehydroepiandrosterone, androstenediol, testosterone, dihydrotestosterone, estrone, estradiol, and estriol.

**[0006]** In some embodiments, the subject has a level of 17-OHP that is less than two times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than two times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than two times an upper limit of a reference range of 17-OHP and a level of A4 that is less than two times an upper limit of a reference range of A4. In some embodiments, the subject has a level of A4 that is less than two times an upper limit of a reference range of A4 and a level of ACTH that is less than two times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.75 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.75 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.75 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.75 times an upper limit of a reference range of A4. In some embodiments, the subject has a level of A4 that is less than 1.75 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.75 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.5 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.5 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.5 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.5 times an upper limit of a reference range of A4. In some embodiments, the subject has a level of A4 that is less than 1.5 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.5 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.25 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.25 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.25 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.25 times an upper limit of a reference range of A4. In some embodiments, the subject has a level of A4 that is less than 1.25 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.25 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than one times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than one times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than one times an upper limit of a reference range of 17-OHP and a level of A4 that is less than one times an upper limit of a reference range of A4. In some embodiments, the subject has a level of A4 that is less than one

times an upper limit of a reference range of A4 and a level of ACTH that is less than one times an upper limit of a reference range of ACTH.

**[0007]** In some embodiments, the methods comprise reducing said dose of said steroid or a pharmaceutically acceptable salt thereof in a 5 mg increment.

**[0008]** In another aspect, the present disclosure provides methods for treating Congenital Adrenal Hyperplasia (CAH). The methods comprise administering a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof to a subject, wherein when said subject has a level of at least one steroid hormone that is more than an upper limit of a reference range of said at least one steroid hormone level, a dose of said steroid or a pharmaceutically acceptable salt thereof is not reduced compared to a dose of said steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient that does not receive said CRF1 antagonist or a pharmaceutically acceptable salt thereof.

**[0009]** In some embodiments, the subject has a level of said at least one steroid hormone that is more than two times an upper limit of a reference range of said at least one steroid hormone level. In some embodiments, the subject has a level of said at least one steroid hormone that is more than 1.75 times an upper limit of a reference range of said at least one steroid hormone level. In some embodiments, the subject has a level of said at least one steroid hormone that is more than 1.5 times an upper limit of a reference range of said at least one steroid hormone level. In some embodiments, the subject has a level of said at least one steroid hormone that is more than 1.25 times an upper limit of a reference range of said at least one steroid hormone level.

**[0010]** In some embodiments, the steroid hormone is selected from the group consisting of adrenocorticotropic hormone (ACTH), androstenedione (A4), 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, dehydroepiandrosterone, androstenediol, testosterone, dihydrotestosterone, estrone, estradiol, and estriol.

**[0011]** In some embodiments, the methods further comprise maintaining said dose of said steroid or a pharmaceutically acceptable salt thereof until said levels of at least two steroid hormones are less than 2 times said upper limit of said reference ranges of said two steroid hormones respectively. In some embodiments, the methods further comprise reducing said dose of said steroid or a pharmaceutically acceptable salt thereof in a 5 mg increment when said levels of at least two steroid hormones are less than 2 times said upper limit of said reference ranges of said two steroid hormones respectively.

**[0012]** In some embodiments, the at least two steroid hormones comprise 17-OHP and ACTH. In some embodiments, the at least two steroid hormones comprise 17-OHP and A4. In some embodiments, the at least two steroid hormones comprise A4 and ACTH. In some embodiments, the reference range of ACTH or A4 level of said subject is controlled by a factor selected from the group consisting of age, sex, menopausal status, laboratory setting, time of a day and combinations thereof.

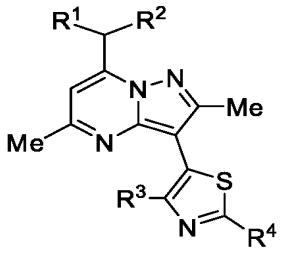
**[0013]** In some embodiments, the level of ACTH or A4 is 2 times, 1.5 times, 1.25 times, or 1 times said upper limit of said normal range of ACTH or A4 level of said subject. In some embodiments, the amount of said steroid or a pharmaceutically acceptable salt thereof comprises a range of about 10 mg to about 80 mg of hydrocortisone equivalents, wherein said steroid or a pharmaceutically acceptable salt thereof is administered daily. In some embodiments, the amount of said $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof comprises a range of about 10 mg to about 200 mg, wherein said $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof is administered daily.

**[0014]** In some embodiments, the subject is treated for a period of about 4 weeks to about 36 weeks.

**[0015]** In some embodiments, the subject is treated for a period of about 4 weeks to about 36 weeks, said subject is reassessed to determine if a different method of treating CAH should be administered.

**[0016]** In some embodiments, the $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003.

**[0017]** In some embodiments, the $CRF_1$ antagonist is a compound of Formula (I):

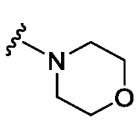
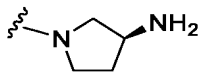
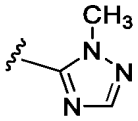
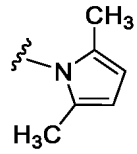



(I),

or a pharmaceutically acceptable salt thereof, wherein:

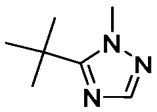
$R^1$ and $R^2$ are independently ethyl or *n*-propyl;

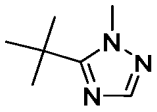
$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

$R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and $R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

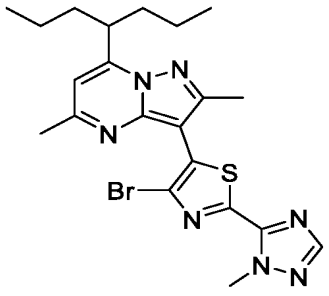
**[0018]** In some embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl.

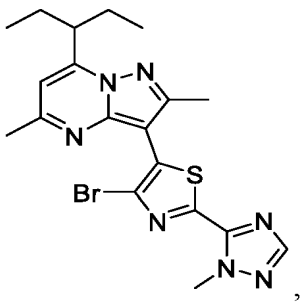
**[0019]** The method of claims 38 or 39, wherein $R^3$ is Cl, Br, or methyl.

**[0020]** In some embodiments, $R^4$ is Br, $R^aR^bN$–, pyridin-4-yl, morpholin-4-yl, or .

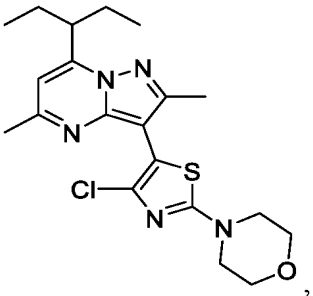
**[0021]** In some embodiments, $R^4$ is morpholin-4-yl or .

**[0022]** In some embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$– and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

**[0023]** In some embodiments the compound is , or a pharmaceutically acceptable salt thereof.

**[0024]** In some embodiments the compound is , or a pharmaceutically acceptable salt thereof.

**[0025]** In some embodiments the compound is



, or a pharmaceutically acceptable salt thereof.

**[0026]** In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg to about 200 mg total daily dose to the subject.

**[0027]** In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject. In some embodiments, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject.

**[0028]** In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject.

**[0029]** In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm to about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μm.

**[0030]** In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

**[0031]** In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

**[0032]** In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further

comprises one or more pharmaceutically acceptable excipients. In some embodiments, the steroid or pharmaceutically acceptable salt thereof is a glucocorticoid or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid or a pharmaceutically acceptable salt thereof is prednisone, cortisone, prednisolone, triamcinolone, methylprednisolone, betamethasone, dexamethasone, hydrocortisone or a pharmaceutically acceptable salt thereof. In some embodiments, the levels of steroid hormones in the subject are determined from a biological sample from the subject. In some embodiments, the biological sample is selected from the group of blood, blood fractions, plasma, serum, and saliva. In some embodiments, the biological sample is obtained non-invasively.

**[0033]** In some embodiments, the subject is tested in the morning. In some embodiments, subject is tested to determine morning levels of A4 and ACTH. In some embodiments, the subject is a pediatric patient. In some embodiments, the subject is from about newborn to about 18 years old.

**[0034]** In some embodiments, the subject is an adult patient. In some embodiments, the steroid and the CRF1 antagonist are administered concurrently. In some embodiments, the steroid and the CRF1 antagonist are administered in one pharmaceutical composition.

**[0035]** In some embodiments, the steroid and the CRF1 antagonist are administered concurrently in separate pharmaceutical compositions. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 24 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 8 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 2 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 10 minutes.

**[0036]** In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

**[0037]** In another aspects, the present disclosure provides compositions comprising a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof, wherein said $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is exogenous glucocorticoids (GC) or a pharmaceutically acceptable salt thereof.

**[0038]** Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

## INCORPORATION BY REFERENCE

**[0039]** All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0040]** The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG."), of which:

**[0041]** FIG. 1 shows the baseline upper limit of a normal range (ULN)/Target Multiples for Serum 17-OHP, ACTH and A4 by subgroup;

**[0042]** FIGS. 2A and 2B illustrate a time matched change of ACTH hormone profile;

**[0043]** FIGS. 3A and 3B illustrate a time matched change of 17-OHP hormone profile; and

**[0044]** FIGS. 4A and 4B illustrate a time matched change of ACTH hormone profile.

## DETAILED DESCRIPTION

**[0045]** While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

**Congenital adrenal hyperplasia**

**[0046]** Congenital adrenal hyperplasia (CAH) is a group of rare inherited autosomal recessive disorders characterized by a deficiency of one of the enzymes needed to make specific hormones. CAH effects the adrenal glands located at the top of each kidney. Normally, the adrenal glands are responsible for producing three different hormones: 1) glucocorticoids, which gauge the body's response to stress, illness or injury; 2) mineralocorticoids, which regulate salt and water levels; and 3) androgens, which are male sex hormones. An enzyme deficiency will make the body unable to produce one or more of these hormones, which in turn will result in the overproduction of another type of hormone precursor in order to compensate for the loss.

**[0047]** The most common cause of CAH is the absence of the enzyme 21-hydroxylase. Different mutations in the gene responsible for 21-hydroxylase result in different levels of the enzyme, producing a spectrum of effects. CAH due to 21-hydroxylase deficiency is responsible for 95% of all cases of CAH and is broken down further into two subcategories: classic CAH, which can be sub-divided into the salt-losing form or the simple-virilizing form, and non-classic CAH. Classic CAH is by far the more severe form and can result in adrenal crisis and death if not detected and treated. Non-classic CAH is milder and may or may not present symptoms. Since the absence of 21-hydroxylase makes these individuals unable to make the hormone cortisol, a glucocorticoid, and, in the case of salt-losing CAH, aldosterone (a mineralocorticoid), the excess steroid precursors, namely 17-hydroxyprogesterone (17-OHP), build up and are shunted down the androgen pathway resulting in excess androgen production which cause a variety of symptoms such as abnormal genital development in infant girls. There are other much rarer forms of CAH as well, including 11-ß hydroxylase deficiency, 17α-hydroxylase deficiency, 3-ß-hydroxysteroid dehydrogenase deficiency, congenital lipoid adrenal hyperplasia and p450 oxidoreductase deficiency which all present different symptoms. CAH patients need adequate care and treatment in order to lead normal lives.

**Corticotropin releasing factor**

**[0048]** Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

**[0049]** CRF has been implicated in psychiatric disorders and neurological diseases including depression and anxiety, as well as the following: Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol and substance abuse and associated withdrawal symptoms, obesity, metabolic syndrome, congenital adrenal hyperplasia (CAH), Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulceration, premenstrual syndrome, sexual dysfunction, premature labor, inflammatory disorders, allergies, multiple sclerosis, visceral pain, sleep disorders, pituitary tumors or ectopic pituitary derived tumors, chronic fatigue syndrome, and fibromyalgia.

**[0050]** CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain thereby suggesting potential functional diversity. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors.

**[0051]** Treatment of CAH is based on normalization of hormone and steroid levels using a variety of chronic medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous Cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which Cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment include cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

**[0052]** The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient cortisol is available during events that may elicit a strong stress response (e.g., intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of Addisonian syndrome due to under-treatment. Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione (A4), testosterone, renin activity, and electrolytes.

**[0053]** Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, absence of the nadir drop in systolic

blood pressure overnight, and insulin resistance. A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the aforementioned adverse outcomes. Treatment of CAH includes efforts to normalize the Cortisol deficiency with glucocorticoids (usually hydrocortisone in children and adults). In some embodiments, there is a need for longer acting and more potent agents with narrow therapeutic indices, such as dexamethasone or prednisolone/prednisone, in adults and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients.

**[0054]** CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotropic hormone ("ACTH"), β-endorphin, and other proopiomelanocortin ("POMC")-derived peptides from the anterior pituitary. Secretion of CRF causes release of ACTH from corticotrophs in the anterior pituitary via binding to the CRF1 receptor, a member of the class B family of G-protein coupled receptors.

**[0055]** Due to the physiological significance of CRF1, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF1 receptor remains a desirable goal and has been the subject of ongoing research and development for the treatment of anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse.

**[0056]** The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21-hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-OHP. Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione (A4), testosterone, and dihydroxytestosterone causing virilization in females. In addition, 21-hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically cortisol and aldosterone. Cortisol is a critical negative

feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

**Certain Definitions**

**[0057]** Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

**[0058]** As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

**[0059]** The term "about" is used to indicate that a value includes 10% level of error for the device or method being employed to determine the value.

**[0060]** The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or."

**[0061]** "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, and preferably having from one to five carbon atoms (i.e. C1-C5alkyl). In some embodiments, an alkyl comprises one to four carbon atoms (i.e., C1-C4alkyl). ). In some embodiments, an alkyl comprises one to three carbon atoms (i.e., C1-C3alkyl). ). In some embodiments, an alkyl comprises one to two carbon atoms (i.e., C1-C2alkyl). In some embodiments, an alkyl comprises one carbon atom (i.e., C1alkyl). In certain embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (n-propyl), 1-methylethyl (iso-propyl), 1-butyl (n-butyl), 1-methylpropyl (sec-butyl), 2-methylpropyl (isobutyl), 1,1-dimethylethyl (tert-butyl), or 1-pentyl (n-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more substituents such as those described herein.

**[0062]** The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that

"comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

**[0063]** "Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. "Administering" a pharmaceutical composition may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

**[0064]** By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

**[0065]** The term "pharmaceutical composition" means a composition comprising at least one active ingredient, such as a steroid or a pharmaceutically acceptable salt thereof or a CRF1 antagonist or a pharmaceutically acceptable salt thereof, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

**[0066]** The term "supraphysiologic amount" describes glucocorticoid dose levels that are above the daily glucocorticoid requirement (production rate) found in healthy individuals.

**[0067]** The term "physiologic amount" describes glucocorticoid dose levels that meet the daily glucocorticoid requirement (production rate) found in healthy individuals.

**[0068]** The term "hydrocortisone equivalents" as used herein is understood by a person skilled in the art to be the conversion calculations needed to be considered when substituting one glucocorticoid for another as the potency and duration of action of various glucocorticoids may vary. Hence, the term "hydrocortisone equivalents" is the standard used for comparison of glucocorticoid potency.

**[0069]** A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the

pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

**[0070]** The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

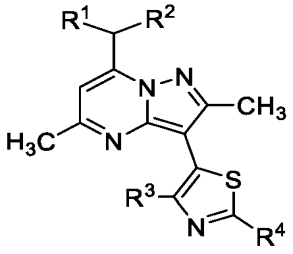
**Compounds**

**[0071]** Disclosed herein are CRF1 antagonists or pharmaceutically acceptable salt thereof such as Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003, and SSR125543.

**[0072]** In one aspect, the CRF1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: N-Butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine hydrochloride (Antalarmin hydrochloride), N-Butyl-N-ethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine hydrochloride (Pfizer CP154526), N-(1-Ethylpropyl)-3,6-dimethyl-2-(2,4,6-trimethylphenox y)-4-pyridinamine hydrochloride (Pfizer CP376395 hydrochloride), 5-Chloro-N-(cyclopropylmethyl)-2-methyl-N-propyl-N'-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride (NBI27914 hydrochloride), (7S)-6-(Cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene hydrochloride (NBI35965 hydrochloride), N-(1-Ethylpropyl)-3-methoxy-5-[2-methoxy-4-

(trifluoromethoxy)phenyl]-6-methyl-2-pyrazinamine hydrochloride (NGD 98-2 hydrochloride), 8-(6-Methoxy-2-methyl-3-pyridinyl)-2,7-dimethyl-N-[(1R)-1-methylpropyl]pyrazolo[1,5-a]-1,3,5-triazin-4-amine (Pexacerfont), 3-[6-(Dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-a]pyrimidin-7-amine hydrochloride (R 121919 hydrochloride), and N-(4-Methoxy-2-methylphenyl)-1-[1-(methoxymethyl)propyl]-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridine-4-amine (SN003), (S)-4-(2-chloro-4-methoxy-5-methylphenyl)-N-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-(prop-2-yn-1-yl)thiazol-2-amine (SSR125543).

**[0073]** Disclosed herein is a compound of Formula (I):



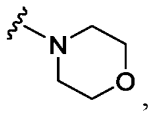
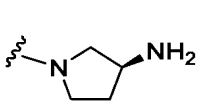
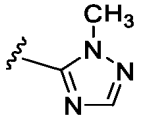
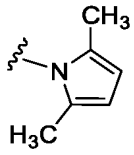
**[0074]**

**[0075]** Formula (I)

**[0076]** or a pharmaceutically acceptable salt thereof, wherein

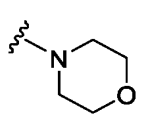
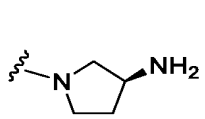
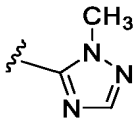
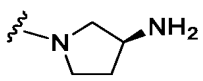
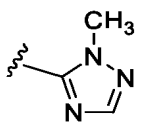
**[0077]** R1 and R2 are independently ethyl or n-propyl;

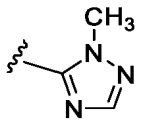
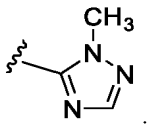
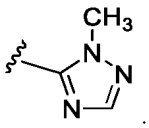
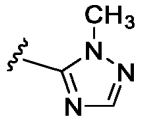
**[0078]** R3 is H, Cl, Br, methyl, trifluoromethyl or methoxy;

**[0079]** R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and

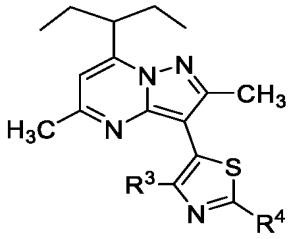
**[0080]** Ra and Rb are independently hydrogen, C1-C3 alkyl, H2NCH2CH2-, (CH3)3COC(O)NHCH2CH2-, or CH3CH2CH2NHCH2CH2.

**[0081]** In some embodiments, R3 is hydrogen, Cl, Br, methyl, or trifluoromethyl. In some embodiments, R3 is hydrogen, Cl, Br, or methyl. In some embodiments, R3 is hydrogen, Cl, or Br. In some embodiments, R3 is hydrogen. In some embodiments, R3 is Cl. In some embodiments, R3 is Br.

**[0082]** In some embodiments, R4 is hydrogen, Br, RaRbN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , ,or . In some embodiments, R4 is Br, RaRbN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, ,or . In some embodiments, R4 is RaRbN–, methoxymethyl, n-

butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or . In some embodiments, R4 is RaRbN–, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or . In some embodiments, R4 is RaRbN–,pyridin-4-yl, morpholin-4-yl, or . In some embodiments, R4 is morpholin-4-yl or . In some embodiments, R4 is RaRbN- and Ra and Rb are independently C1-C3alkyl.

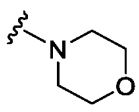
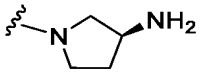
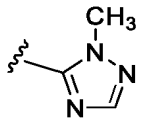
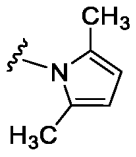
**[0083]** Disclosed herein is a compound of Formula (II):



**[0084]** Formula (II)

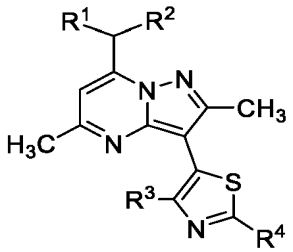
**[0085]** or a pharmaceutically acceptable salt thereof, wherein

**[0086]** R3 is H, Cl, Br, methyl, trifluoromethyl or methoxy;

**[0087]** R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and

**[0088]** Ra and Rb are independently hydrogen, C1-C3 alkyl, H2NCH2CH2-, (CH3)3COC(O)NHCH2CH2-, or CH3CH2CH2NHCH2CH2.

**[0089]** Disclosed herein is a compound of Formula (III):

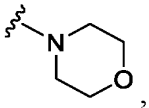
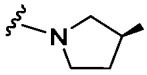
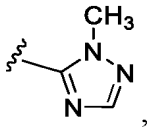
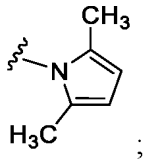


**[0090]** Formula (III)

**[0091]** or a pharmaceutically acceptable salt thereof, wherein

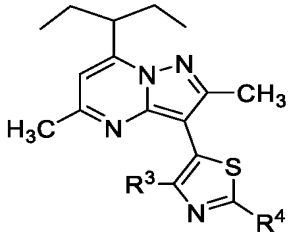
**[0092]** R1 and R2 are n-propyl;

**[0093]** R3 is H, Cl, Br, methyl, trifluoromethyl or methoxy;

**[0094]** R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and

**[0095]** Ra and Rb are independently hydrogen, C1-C3 alkyl, H2NCH2CH2-, (CH3)3COC(O)NHCH2CH2-, or CH3CH2CH2NHCH2CH2.

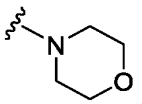
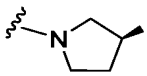
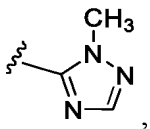
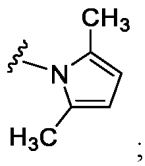
**[0096]** Disclosed herein is a compound of Formula (IV):



**[0097]** Formula IV

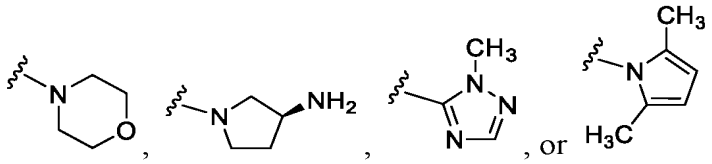
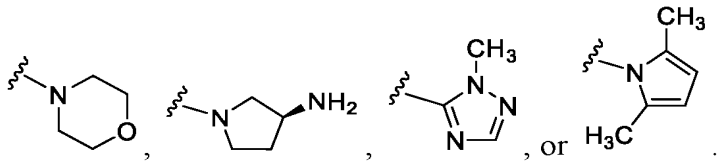
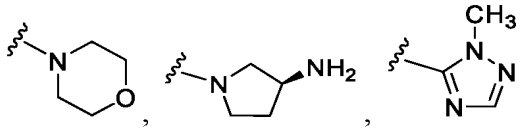
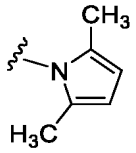
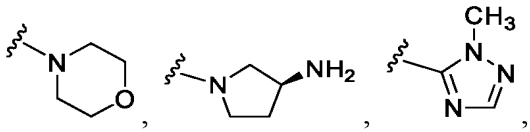
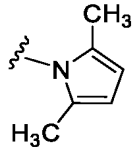
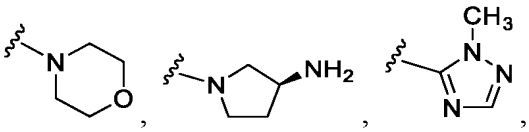
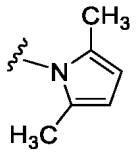
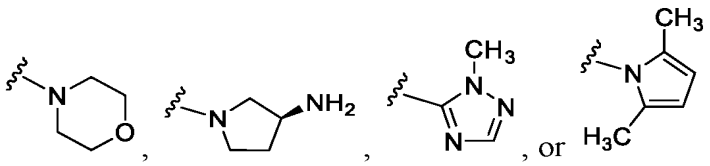
**[0098]** or a pharmaceutically acceptable salt thereof, wherein

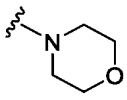
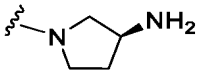
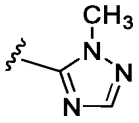
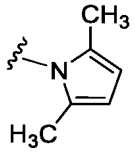
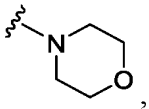
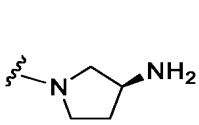
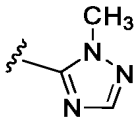
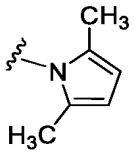
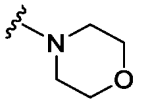
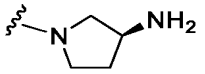
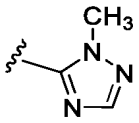
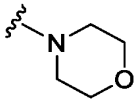
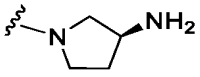
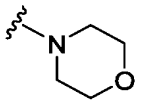
**[0099]** R3 is Cl, Br, methyl, trifluoromethyl or methoxy;

**[0100]** R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and

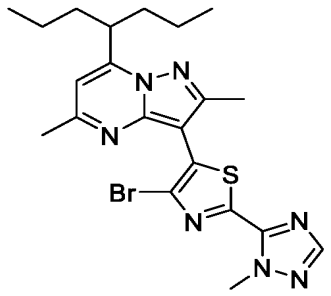
**[0101]** Ra and Rb are independently hydrogen, C1-C3 alkyl, H2NCH2CH2-, (CH3)3COC(O)NHCH2CH2-, or CH3CH2CH2NHCH2CH2.

**[0102]** For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be Cl, Br, methyl, trifluoromethyl, or methoxy. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be Cl, Br, methyl, or trifluoromethyl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be Cl, Br, or methyl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be Cl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be Br. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be methyl.

**[0103]** For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is Br, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is Br, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is Br, acetamido, pyridin-4-yl, morpholin-4-yl, , . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is Br, pyridin-4-yl, morpholin-4-yl, , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is pyridin-4-yl, morpholin-4-yl, . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is

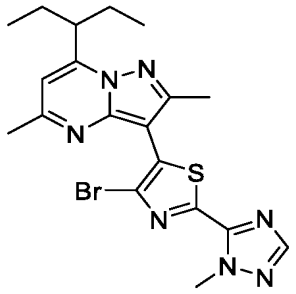
morpholin-4-yl, , , , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is , , , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is , , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is , or . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is .

**[0104]** Disclosed herein is 3-[4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]pyrimidine or a pharmaceutically acceptable salt thereof:



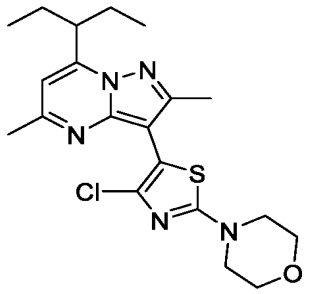
Compound 1

**[0105]** Disclosed herein is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine or a pharmaceutically acceptable salt thereof:



Compound 2

**[0106]** Disclosed herein is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine (or alternatively 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine), a pharmaceutically acceptable salt thereof:



Compound 3.

**[0107]** In some embodiments, 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine is referred to as Compound 3. In some embodiments, 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine is referred to as Compound 3.

**[0108]** In one aspect, the CRF1 antagonist or pharmaceutically acceptable salt thereof may be an astressin. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

**Pharmaceutical Compositions**

**[0109]** Disclosed herein are pharmaceutical compositions comprising a compound or pharmaceutically acceptable salt described herein. In certain embodiments, the composition comprises a steroid or a pharmaceutically acceptable salt thereof and a $CRF_1$ antagonist or pharmaceutically acceptable salt thereof as disclosed above. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is exogenous glucocorticoids (GC) or a pharmaceutically acceptable salt thereof.

***Dosage Form***

**[0110]** In some embodiments, the pharmaceutical compositions described herein are provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing

an amount of a compound or pharmaceutically acceptable salt described herein that is suitable for administration to an animal, preferably mammal, subject in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

**[0111]** Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

**[0112]** In some embodiments, the pharmaceutical compositions described herein are formulated as oral dosage forms. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules. In some embodiments, the pharmaceutical composition comprises one or more additional pharmaceutically acceptable excipients. See, e.g., Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005) for a list of pharmaceutically acceptable excipients.

***Capsule***

**[0113]** In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

**[0114]** In some embodiments, the capsule is formed using materials which include, but are not limited to, natural or synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, or any combinations thereof. In some embodiments, the capsule is formed using preservatives, coloring and opacifying agents, flavorings and sweeteners, sugars, gastroresistant substances, or any combinations thereof. In some embodiments, the capsule is coated. In some embodiments, the coating covering the capsule includes, but is not limited to, immediate release coatings, protective coatings, enteric or

delayed release coatings, sustained release coatings, barrier coatings, seal coatings, or combinations thereof. In some embodiments, a capsule herein is hard or soft. In some embodiments, the capsule is seamless. In some embodiments, the capsule is broken such that the particulates are sprinkled on soft foods and swallowed without chewing. In some embodiments, the shape and size of the capsule also vary. Examples of capsule shapes include, but are not limited to, round, oval, tubular, oblong, twist off, or a non-standard shape. The size of the capsule may vary according to the volume of the particulates. In some embodiments, the size of the capsule is adjusted based on the volume of the particulates and powders. Hard or soft gelatin capsules may be manufactured in accordance with conventional methods as a single body unit comprising the standard capsule shape. A single-body soft gelatin capsule typically may be provided, for example, in sizes from 3 to 22 minims (1 minims being equal to 0.0616 ml) and in shapes of oval, oblong or others. The gelatin capsule may also be manufactured in accordance with conventional methods, for example, as a two-piece hard gelatin capsule, sealed or unsealed, typically in standard shape and various standard sizes, conventionally designated as (000), (00), (0), (1), (2), (3), (4), and (5). The largest number corresponds to the smallest size. In some embodiments, the pharmaceutical composition described herein (e.g., capsule) is swallowed as a whole.

**[0115]** In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients. In some embodiments, the capsule is free of additional excipients.

**[0116]** In some embodiments, a capsule is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the capsule has a dose strength of up to 200 mg. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus II.

***Tablet***

**[0117]** Poorly soluble drugs may be difficult to formulate using standard technologies such as high shear wet granulation. Optimum delivery of poorly soluble drugs may require complex technologies such as solid solutions amorphous dispersions (hot melt extrusion or spray drying), nano-formulations or lipid-based formulations. Hydrophobic drug substances may be considered poorly soluble according to USP criteria and may be known to be difficult to granulate with water and other excipients. This is likely due to most known excipients for immediate release formulations being water soluble or water-swellable. Making a tablet of a high dose drug substance that is poorly soluble may require a high concentration of the drug substance.

However, as the drug concentration is increased above a certain level, formation of granules may become more and more difficult. Furthermore, at a certain drug load, it may become impossible.

**[0118]** In some embodiments, the pharmaceutical composition is formulated as a tablet.

**[0119]** In some embodiments, the tablet is made by compression, molding, or extrusion, optionally with one or more pharmaceutically acceptable excipient. In some embodiments, compressed tablets are prepared by compressing a compound or pharmaceutically acceptable salt described herein in a free-flowing form, optionally mixed with pharmaceutically acceptable excipients. In some embodiments, molded tablets are made by molding a mixture of the powdered a compound or pharmaceutically acceptable salt described herein, moistened with an inert liquid diluent. In some embodiments, the tablet is prepared by hot-melt extrusion. In some embodiments, extruded tablets are made by forcing a mixture comprising a compound or pharmaceutically acceptable salt described herein, through an orifice or die under controlled conditions. In some embodiments, the tablet is coated or scored. In some embodiments, the tablet is formulated so as to provide slow or controlled release of a compound or pharmaceutically acceptable salt described herein. In some embodiments, a tablet is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the tablet has a dose strength of up to 200 mg. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus II.

**[0120]** In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg or less than about 200 mg. In some embodiments, the tablet has a dose strength of more than about 50 mg, more than about 100 mg, more than about 150 mg, more than about 200 mg, or more than about 250 mg. In some embodiments, the tablet size is less than about 1000 mg for a dose strength of more than about 50 mg. In some embodiments, the tablet size is less than 800 mg for a dose strength of more than about 100 mg. In some embodiments, the tablet size is less than 600 mg for a dose strength of more than about 150 mg. In some embodiment, the tablet size is less than 400 mg for a dose strength of more than about 200 mg. In some embodiments, the tablet size is less than 400 mg for a dose strength of 200 mg.

**[0121]** In some embodiments, more than about 20% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about

60% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 24 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 12 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 6 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 3 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 2 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than 70% of the tablet is dissolved in 60 minutes in conventional dissolution media.

**[0122]** In some embodiments, the tablet is produced at a commercial scale.

**[0123]** In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

**[0124]** In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete dry powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone,

polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

***Pharmaceutically Acceptable Excipients***

**[0125]** In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient. In some embodiments, the composition is free of pharmaceutically acceptable excipients. The term "pharmaceutically acceptable excipient", as used herein, means one or more compatible solid or encapsulating substances, which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction, which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. In some embodiments, the pharmaceutically acceptable excipient is of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal, being treated.

**[0126]** Some examples of substances, which can serve as pharmaceutically acceptable excipients include:

- Amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, the amino acid is arginine. In some embodiments, the amino acid is L-arginine.
- Monosaccharides such as glucose (dextrose), arabinose, mannitol, fructose (levulose), and galactose.
- Cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose.
- Solid lubricants such as talc, stearic acid, magnesium stearate, and sodium stearyl fumarate.
- Polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol.
- Emulsifiers such as the polysorbates.
- Wetting agents such as sodium lauryl sulfate, Tween®, Span , alkyl sulphates, and alkyl ethoxylate sulphates.

- Diluents such as calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose.
- Binders such as starches (corn starch and potato starch), gelatin, sucrose, hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC).
- Disintegrants such as starch, and alginic acid.
- Super-disintegrants such as ac-di-sol, croscarmellose sodium, sodium starch glycolate and crospovidone.
- Glidants such as silicon dioxide.
- Coloring agents such as the FD&C dyes.
- Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors.
- Preservatives such as benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate, phenylmercuric nitrate, parabens, and sodium benzoate.
- Tonicity adjustors such as sodium chloride, potassium chloride, mannitol, and glycerin.
- Antioxidants such as sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA.
- pH adjuster such as NaOH, sodium carbonate, sodium acetate, HCl, and citric acid.
- Cryoprotectants such as sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran.
- Cationic surfactants such as cetrimide, benzalkonium chloride and cetylpyridinium chloride.
- Anion surfactants such as alkyl sulphates, alkyl ethoxylate sulphates, soaps, carboxylates, sulfates, and sulfonates.
- Non-ionic surfactants such as polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glyol esters, glycerol esters, sorbitan derivatives, polyethylene glycol (PEG-40, PEG-50, PEG-55), and ethers of fatty alcohols.
- Organic materials such as carbohydrate and modified carbohydrates, lactose, a-lactose monohydrate, spray dried lactose and anhydrous lactose, starch and pre-gelatinized starch, sucrose, manitol, sorbitol, cellulose, powdered cellulose and microcrystalline cellulose.

- Inorganic materials such as calcium phosphates (anhydrous dibasic calcium phosphate, dibasic calcium phosphate and tribasic calcium phosphate).
- Co-processed diluents.
- Surfactants such as sodium lauryl sulfate.
- Compression aids.
- Anti-tacking agents such as silicon dioxide and talc

***Amounts***

**[0127]** In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 400 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 300 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 200 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 100 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 90 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 80 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 70 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 60 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 50 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 40 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 30 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 20 mg

of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 10 mg of a compound or pharmaceutically acceptable salt described herein.

**[0128]** In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 200 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 100 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 90 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 80 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 70 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 60 mg of a compound or pharmaceutically acceptable salt described herein f. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 50 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 40 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 30 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 20 mg of a compound or pharmaceutically acceptable salt described herein.

***Particle size***

**[0129]** In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises a compound or pharmaceutically acceptable salt described herein, in the form

of microparticles. In some embodiments, the microparticles have an average size from about 1 μm to about 100 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 50 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 30 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 20 μm. In some embodiments, the microparticles have an average size from about 5 μm to about 15 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 10 μm. In some embodiments, the microparticles have an average size from about 3 μm to about 10 μm. In some embodiments, the microparticles have an average size from about 4 μm to about 9 μm.

**Methods of Treatment**

**[0130]** Disclosed herein are methods of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a compound or pharmaceutically acceptable salt described herein. In some embodiments, the methods described herein result in the reduction of a level of a hormone. Such hormones include deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, 17-OHP, dehydroepiandrosterone, androstenediol, A4, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and ACTH. In some embodiments, the methods described herein result in the reduction of 17-OHP levels. In some embodiments, the methods described herein result in the reduction of A4 levels. In some embodiments, the methods described herein result in the reduction of ACTH levels, also known as corticotropin.

**[0131]** Further, in some embodiments, the methods described herein result in the maintenance of the reduction of 17-OHP, A4, and/or ACTH levels. In some embodiments, the reductions of 17-OHP, A4, and/or ACTH levels may last for at least 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 2 years, 5 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years, or 100 years.

**[0132]** Moreover, the present disclosure provides different patient subtype regimens for treating Congenital Adrenal Hyperplasia (CAH) patients. In one aspect, the present disclosure provides a method of treating Congenital Adrenal Hyperplasia (CAH), comprising administering

an effective amount of a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof to a subject, i.e., a CAH patient/individual, over a 24 hour period, which the effective amount of the steroid is dependent on the levels of steroid hormones, such as ACTH, A4, 17-OHP, or any combinations thereof, of the subject measured at the time of beginning the treatment of CAH, typically in the am. Prior to implementing the method of treatment disclosed herein, a CAH patient may be evaluated to determine the patient's plasma steroid hormone levels.

**[0133]** Generally, a normal range, a normal laboratory reference range, or a reference range of ACTH level or A4 level in a subject may be broad and dependent on many different factors. For example, ACTH, 17-OHP or A4 is secreted in bursts with a daily rhythm in a subject. Plasma samples collected at 8 am in the morning may show different range of ACTH or A4 levels in a subject compared to plasma samples collected at 2 pm, 4 pm, or midnight during the day. Further, the normal range of ACTH or A4 levels are dependent on a factor such as laboratory setting. Laboratory setting may comprise different types of assays for detecting ACTH or A4 levels, equipment utilized in the laboratory, personnel in the laboratory performing the assays, and different batches of reagents used during the assays. Different ages of a subject may provide different normal ranges of ACTH or A4 levels as well. Moreover, a normal range of ACTH level or A4 level in a subject may be dependent on the sex of the subject. For example, not meant to be limiting, a male subject's normal range of ACTH level may be from 7 to 63.3 pg/mL, as assessed in the am, typically before 10 am, and A4 level, also assessed in the am, typically before 10 am, may be from 50 to 220 ng/dL for males aged 18 to 30 years, from 40 to 190 ng/dL for males aged 31 to 50 years and from 50 to 220 ng/dL for males aged 51 to 60 years. Additionally, a normal range of ACTH level or A4 level in a female subject may be dependent on the female subject's menopausal stage. For example, not meant to be limiting, a pre-menopausal female subject's normal range of ACTH level may be from 7 to 63 pg/mL, as assessed in the am, typically before 10 am, and A4 level may be from 51 to 213 ng/dL for women in the mid-follicular stage, from 73 to 230 ng/dL for women in the surge stage, from 73 to 184 for women in the mid luteal stage. A post-menopausal female subject's normal range of ACTH level may be from 7 to 63.3 pg/mL and A4 level may be from 20 to 75 ng/dL. Normal ranges for PM assessments of ACTH and A4 have not been established.

**[0134]** In some embodiments, when a subject has levels that are less than two (2) times an upper limit of the normal ranges or the normal laboratory reference ranges of ACTH and A4 level respectively, a percentage of the total daily GC dose, typically done in 5 mg hydrocortisone equivalents, of the effective amount of the steroid or a pharmaceutically acceptable salt thereof is reduced compared to a dose of the effective amount of the steroid or a pharmaceutically

acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has a level that is less than 2 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is less than 1.75 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is less than 1.5 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is less than 1.25 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is less than 1.0 times the upper limit of the normal range of ACTH or A4 level.

**[0135]** In certain embodiments, as long as the levels of both the ACTH and A4 are less than 2 times an upper limit of the normal reference ranges of ACTH and A4 respectively, the dosage of the steroid or a pharmaceutically acceptable salt thereof is reduced. For example, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1.75 times the upper limit of the normal range of ACTH and A4 level is less than 1.25 the upper limit of the normal range of A4. Further, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1.25 times the upper limit of the normal range of ACTH and A4 level is less than 1.5 the upper limit of the normal range of A4. Moreover, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1.5 times the upper limit of the normal range of ACTH and A4 level is less than 1.5 the upper limit of the normal range of A4. Additionally, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1.25 times the upper limit of the normal range of ACTH and A4 level is less than 1.25 the upper limit of the normal range of A4.The regimen of treating with reduced amount of the steroid or a pharmaceutically acceptable salt thereof compared to the amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof may be utilized. The reduction of GC daily does may be done in a 5 mg hydrocortisone equivalents, 4 mg hydrocortisone equivalents, 3 mg hydrocortisone equivalents, 2 mg hydrocortisone equivalents, 1 mg hydrocortisone equivalents, or 0.5 mg hydrocortisone equivalents.

**[0136]** In some embodiments, when a subject has levels that are less than two (2) times an upper limit of the normal ranges or the normal laboratory reference ranges of ACTH and 17-OHP level respectively, a percentage of the total daily GC dose, typically done in 5 mg hydrocortisone equivalents, of the effective amount of the steroid or a pharmaceutically acceptable salt thereof is reduced compared to a dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e.,

a compound disclosed herein) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has a level that is less than 2 times the upper limit of the normal range of ACTH or 17-OHP level. In some embodiments, the subject has a level that is less than 1.75 times the upper limit of the normal range of ACTH or 17-OHP level. In some embodiments, the subject has a level that is less than 1.5 times the upper limit of the normal range of ACTH or 17-OHP level. In some embodiments, the subject has a level that is less than 1.25 times the upper limit of the normal range of ACTH or 17-OHP level. In some embodiments, the subject has a level that is less than 1.0 times the upper limit of the normal range of ACTH or 17-OHP level. As long as the levels of both the ACTH and 17-OHP are less than 2 times an upper limit of the normal reference ranges of ACTH and 17-OHP respectively, the dosage of the steroid or a pharmaceutically acceptable salt thereof is reduced. For example, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1.5 times the upper limit of the normal range of ACTH and 17-OHP level is less than 1.75 the upper limit of the normal range of 17-OHP. Further, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1 times the upper limit of the normal range of ACTH and 17-OHP level is less than 1.25 the upper limit of the normal range of 17-OHP. The regimen of treating with reduced amount of the steroid or a pharmaceutically acceptable salt thereof compared to the amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof may be utilized.

**[0137]** In some embodiments, when a subject has levels that are less than two (2) times an upper limit of the normal ranges or the normal laboratory reference ranges of A4 and 17-OHP level respectively, a percentage of the total daily GC dose, typically done in 5 mg hydrocortisone equivalents, of the effective amount of the steroid or a pharmaceutically acceptable salt thereof is reduced compared to a dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has a level that is less than 2 times the upper limit of the normal range of A4 or 17-OHP level. In some embodiments, the subject has a level that is less than 1.75 times the upper limit of the normal range of A4 or 17-OHP level. In some embodiments, the subject has a level that is less than 1.5 times the upper limit of the normal range of A4 or 17-OHP level. In some embodiments, the subject has a level that is less than 1.25 times the upper limit of the normal range of A4 or 17-OHP level. In some embodiments, the subject has a level that is less than 1.0 times the upper limit of the normal range of A4 or 17-OHP level. As long as the levels of both the A4 and 17-OHP are less than 2 times an upper limit of the normal reference ranges of

A4 and 17-OHP respectively, the dosage of the steroid or a pharmaceutically acceptable salt thereof is reduced. For example, a CAH patient's biological sample may be measured to show that the patient's A4 level is less than 1 times the upper limit of the normal range of A4 and 17-OHP level is less than 1.75 the upper limit of the normal range of 17-OHP. Further, a CAH patient's biological sample may be measured to show that the patient's A4 level is less than 1.5 times the upper limit of the normal range of A4 and 17-OHP level is less than 1.25 the upper limit of the normal range of 17-OHP. The regimen of treating with reduced amount of the steroid or a pharmaceutically acceptable salt thereof compared to the amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof may be utilized.

**[0138]** When a CRF1 antagonist is not administered, treatment of CAH patients needs to replace the cortisol deficiency and normalize the excess androgen production, which is a sequalae of the enzymatic deficiency in CAH, by administering exogenous glucocorticoids (GC) at a dose that is usually well above the normal physiologic does used for cortisol replacement in patients with other diseases, such as Addison's disease. Reduced levels of exposure to steroids, form supraphysiologic to physiologic levels, may be beneficial to CAH patients. In some embodiments, a dose of about 10 mg to about 80 mg GC is administered to a CAH patient when a CRF1 antagonist is not administered. In some embodiments, the dose of GC is administered to CAH patients one time, two times, three times, or four times daily.

**[0139]** For example, not meant to be limiting, a dose of about 80mg GC could be administered to a CAH patient when a CRF1 antagonist is not administered. If this CAH patient's ACTH level and A4 level are less than 2, 1.5, or 1.25 times the upper limit of the normal range of ACTH level and A4 levels respectively after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80mg GC may be reduced in a 5 mg hydrocortisone equivalent increment when administered together with the CRF1 antagonist (i.e., a compound disclosed herein). In some embodiments, a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof in a dose of about 10 mg to about 200 mg total daily dose is administered to the subject. The CAH patient may be receiving a dose of 75 mg GC during the treatment regimen when the compound is administered together. After a certain period, when the CAH patient's ACTH level and A4 levels remain less than 2, 1.5, or 1.25 times the upper limit of the normal range of the ACTH and A4 levels respectively, the dose of 75 mg GC may be further reduced in a 5 mg increment to 70 mg when administered with the CRF1 antagonist. The dose of the GC may be continuously reduced in a 5 mg increment hydrocortisone equivalent when administered together with the CRF1 antagonist, over a 24 hour

period, until the subject's ACTH or A4 level is not less than 2, 1.5, or 1.25 times the upper limit of the normal range of ACTH or A4 level.

**[0140]** Moreover, if this CAH patient's ACTH level is less than 1.75 times the upper limit of the normal range of ACTH level and A4 level is less than 1.5 times the upper limit of the normal range of A4 level after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80mg GC may be reduced in a 5 mg increment when administered together the CRF1 antagonist (i.e., a compound disclosed herein). If this CAH patient's ACTH level is less than 1.5 times the upper limit of the normal range of ACTH level and A4 level is less than 1.75 times the upper limit of the normal range of A4 level after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80mg GC may be reduced in a 5 mg increment when administered together the CRF1 antagonist (i.e., a compound disclosed herein). If this CAH patient's ACTH level is less than 1.25 times the upper limit of the normal range of ACTH level and A4 level is less than 1.25 times the upper limit of the normal range of A4 level after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80mg GC may be reduced in a 5 mg increment when administered together the CRF1 antagonist (i.e., a compound disclosed herein). In some embodiments, if this CAH patient's ACTH level is less than 1.0 times the upper limit of the normal range of ACTH level and A4 level is less than 1.0 times the upper limit of the normal range of A4 level after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80mg GC may be reduced in a 5 mg increment when administered together with the CRF1 antagonist (i.e., a compound disclosed herein).

**[0141]** In some embodiments, the subject will be treated for a period of about 1 week to about 40 weeks. In some embodiments, the subject will be treated for a period of about 2 weeks to about 39 weeks. In some embodiments, the subject will be treated for a period of about 3 weeks to about 38 weeks. In some embodiments, the subject will be treated for a period of about 4 weeks to about 36 weeks. In some embodiments, if a subject has been treated for a period of time described herein and has levels of A4 and ACTH less than the lower limit of the normal laboratory reference range, the subject may continue with steroid reduction until the subject maintain hormone levels consistently within the normal range of A4 and ACTH.

**[0142]** Further, in some embodiments, when a subject has a level that is more than an upper limit of the normal range or the normal laboratory reference range of ACTH or A4 level, the total daily dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof is not reduced compared to a dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof. In some

embodiments, the subject has a level that is more than 2 times the upper limit of the normal range of ACTH or A4 level. Some subjects may further be categorized as having severe control issues when the subjects have more than 4 times an upper limit of the normal range of both ACTH and A4 levels. Moreover, some subjects may be further categorized as having moderate control issues when the subjects have more than 2 times the upper limit of normal range of the ACTH level but less than 4 times the upper limit of normal range of the A4 level. In some embodiments, the subject has a level that is more than 1.75 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is more than 1.5 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is more than 1.25 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is more than 1.0 times the upper limit of the normal range of ACTH or A4 level.

**[0143]** Additionally, in some embodiments, when a subject has an ACTH level that is more than an upper limit of the normal range or the normal laboratory reference range of ACTH level and an A4 level that is more than an upper limit of the normal range or the normal laboratory reference range of A4, the total daily dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof is not reduced compared to a dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has an ACTH level that is more than 1.75 times the upper limit of the normal range of ACTH and an A4 level that is more than 1.5 times the upper limit of the normal range of A4. In some embodiments, the subject has an ACTH level that is more than 1.5 times the upper limit of the normal range of ACTH and an A4 level that is more than 1.25 times the upper limit of the normal range of A4. In some embodiments, the subject has an ACTH level that is more than 1.25 times the upper limit of the normal range of ACTH and an A4 level that is more than 1 times the upper limit of the normal range of A4. In some embodiments, the subject has an ACTH level that is more than 1 times the upper limit of the normal range of ACTH and an A4 level that is more than 1.25 times the upper limit of the normal range of A4. In some embodiments, the subject has an ACTH level that is more than 1.25 times the upper limit of the normal range of ACTH and an A4 level that is more than 1.5 times the upper limit of the normal range of A4. In some embodiments, the subject has an ACTH level that is more than 1.5 times the upper limit of the normal range of ACTH and an A4 level that is more than 1.75 times the upper limit of the normal range of A4.

**[0144]** In some embodiments, a dose of about 10 mg to about 80 mg GC is administered to a CAH patient when a CRF1 antagonist is not administered. In some embodiments, the dose of

GC is administered to CAH daily one time, two times, three times, or four times. In some embodiments, a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof in a dose of about 10 mg to about 200 mg total daily dose is administered to the subject. For example, not meant to be limiting, a dose of about 80 mg GC administered to a CAH patient when a CRF1 antagonist is not administered. If this CAH patient's ACTH level or A4 level is more than the upper limit of the normal range of ACTH level or A4 level after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80 mg GC may be maintained when administered together the CRF1 antagonist (i.e., a compound disclosed herein). Further, if this CAH patient's ACTH level and A4 levels are more than the upper limit of the normal range of ACTH level and A4 level respectively after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80 mg GC may be maintained when administered together the CRF1 antagonist (i.e., a compound disclosed herein).

**[0145]** During the treatment of administering the maintained dose of GC together with the CRF1 antagonist, the CAH patient's ACTH and A4 levels are monitored. In some embodiments, as soon as the CAH patient's ACTH and A4 level become less than 2 times the upper limit of the normal range of the ACTH and A4 level respectively, the dose of GC may be reduced in a 5 mg hydrocortisone equivalent increment to the CAH patient when administered together with the CRF1 antagonist. In some embodiments, as soon as the CAH patient's ACTH and A4 levels become less than 1.75 times the upper limit of the normal range of the ACTH and A4 level respectively, the dose of GC may be reduced in a 5 mg hydrocortisone equivalent increment to the CAH patient when administered together with the CRF1 antagonist. In some embodiments, as soon as the CAH patient's ACTH and A4 levels become less than 1.5 times the upper limit of the normal range of the ACTH and A4 level respectively, the dose of GC may be reduced in a 5 mg hydrocortisone equivalent increment to the CAH patient when administered together with the CRF1 antagonist. In some embodiments, as soon as the CAH patient's ACTH and A4 levels become less than 1.25 times the upper limit of the normal range of the ACTH and A4 levels respectively, the dose of GC may be reduced in a 5 mg hydrocortisone equivalent increment to the CAH patient when administered together with the CRF1 antagonist. In some embodiments, as soon as the CAH patient's ACTH and A4 levels become less than 1.0 times the upper limit of the normal range of the ACTH and A4 levels respectively, the dose of GC may be reduced in a 5 mg hydrocortisone equivalent increment to the CAH patient when administered together with the CRF1 antagonist. Moreover, the dose of the GC may be continuously reduced in a 5 mg increment when administered together with the CRF1 antagonist until the subject's ACTH and A4 levels are not less than 2, 1.5, or 1.25 times the upper limit of the normal range of ACTH and A4 levels respectively.

**[0146]** In some embodiments, the subject will be treated for a period of about 1 week to about 40 weeks. In some embodiments, the subject will be treated for a period of about 2 weeks to about 39 weeks. In some embodiments, the subject will be treated for a period of about 3 weeks to about 38 weeks. In some embodiments, the subject will be treated for a period of about 4 weeks to about 36 weeks. In some embodiments, after the subject has been treated for a period of time described herein, the subject may be reassessed to determine whether a different patient subtype regimen may be applicable.

**[0147]** In some embodiments, the dose of steroid or a pharmaceutically acceptable salt thereof is in a dose of about 10 mg to about 80 mg of hydrocortisone equivalents. In some embodiments, the steroid is a glucocorticoid or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is tested in the morning to determine morning levels of A4 and ACTH.

**[0148]** With specificity provided from a particular laboratory setting, in some embodiments, two times the upper limit of the normal laboratory reference range of A4 for a male subject is more than about 440 ng/dl, more than about 430 ng/dl, more than about 420 ng/dl, more than about 410 ng/dl, more than about 400 ng/dl, more than about 390 ng/dl, more than about 380 ng/dl, more than about 370 ng/dl. In some embodiments, the normal laboratory reference range of A4 for a male subject is from about 40 ng/dl to about 190 ng/dl. In some embodiments, the normal laboratory reference range of A4 for a male subject is from about 50 ng/dl to about 220 ng/dl.

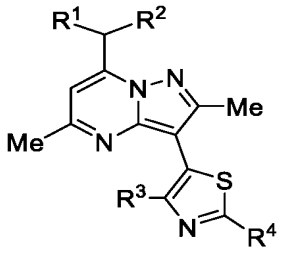
**[0149]** In some embodiments, two times the upper limit of the normal laboratory reference range of A4 for a female subject is more than about 560 ng/dl, more than about 550 ng/dl, more than about 540 ng/dl, more than about 530 ng/dl, more than about 520 ng/dl, more than about 510 ng/dl, 500 ng/dl, more than about 490 ng/dl, more than about 480 ng/dl, more than about 470 ng/dl, more than about 460 ng/dl, more than about 450 ng/dl, more than about 430 ng/dl, more than about 420 ng/dl, more than about 410 ng/dl, 400 ng/dl, more than about 390 ng/dl, more than about 380 ng/dl, more than about 370 ng/dl, more than about 360 ng/dl, more than about 350 ng/dl, or more than about 340 ng/dl. In some embodiments, the normal laboratory reference range of A4 for a female subject is from about 51 ng/dl to about 213 ng/dl. In some embodiments, the normal laboratory reference range of A4 for a female subject is from about 73 ng/dl to about 230 ng/dl. In some embodiments, the normal laboratory reference range of A4 for a female subject is from about 73 ng/dl to about 184 ng/dl.

**[0150]** In some embodiments, two time the upper limit of the normal laboratory reference of ACTH is more than about 110 pg/dl, more than about 120 pg/dl, more than about 130 pg/dl,

more than about 140 pg/dl, or more than about 150 pg/dl. In some embodiments, the normal laboratory reference range of ACTH is from about 7 pg/dl to about 70 pg/dl.

**[0151]** In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003.

**[0152]** In some embodiments, the $CRF_1$ antagonist is a compound of Formula (I):

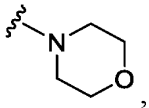
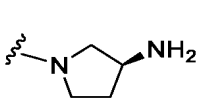
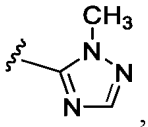
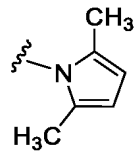



(I),

or a pharmaceutically acceptable salt thereof, wherein:

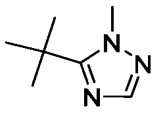
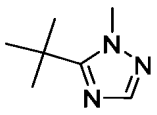
$R^1$ and $R^2$ are independently ethyl or *n*-propyl;

$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

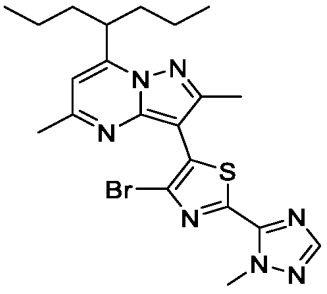
$R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and

$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

**[0153]** In some embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl. In some embodiments, $R^3$ is Cl, Br, or methyl.

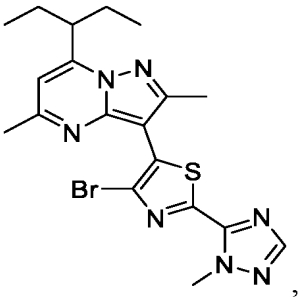
**[0154]** In some embodiments, $R^4$ is Br, $R^aR^bN$–, pyridin-4-yl, morpholin-4-yl, or . In some embodiments, $R^4$ is morpholin-4-yl or . In some embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$– and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

**[0155]** In some embodiments, the compound is



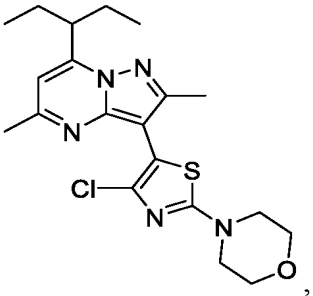

, or a pharmaceutically acceptable salt thereof.

**[0156]** In some embodiments, the compound is




, or a pharmaceutically acceptable salt thereof.

**[0157]** In some embodiments, the compound is




, or a pharmaceutically acceptable salt thereof.

**[0158]** In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg to about 200 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

**[0159]** In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 40 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 30 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 20 mg

total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 15 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg total daily dose to the subject.

**[0160]** In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm to about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μ.

**[0161]** In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

**[0162]** In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

**[0163]** In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

**[0164]** In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 1 to about 8 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 to about 7 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 to about 6 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 3 to about 5 hours in a subject.

**[0165]** In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 8 hours in a subject. In some

embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 7 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 6 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 5 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 4 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 3 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 1 hour in a subject.

**[0166]** In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof once a month, twice a month, three times a month, once a week, twice a week, three times a week, once every two days, once a day, twice a day, three times a day, or four times a day. In some embodiments, the methods described herein administer CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof twice a day.

**[0167]** In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1500 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1400 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1300 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1100 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 900 mg/day. In some embodiments, Compound 1 is

administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 60 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 70 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 80 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 90 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 700 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 150 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 500 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 400 mg/day.

**[0168]** In some embodiments, Compound 1 is administered at a dose of about 500 mg/day. In some embodiments, Compound 1 is administered at a dose of about 400 mg/day. In some embodiments, Compound 1 is administered at a dose of about 300 mg/day. In some embodiments, Compound 1 is administered at a dose of about 200 mg/day. In some embodiments, Compound 1 is administered at a dose of about 100 mg/day.

**[0169]** In some embodiments, about 100 mg to about 1600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 800 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is

administered per day. In some embodiments, about 200 mg to about 600 mg of CRF1 antagonist or pharmaceutically acceptable salt is administered per day. In some embodiments, about 300 mg to about 600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

**[0170]** In some embodiments, less than about 2000 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1200 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1000 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 800 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 600 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 500 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 400 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 300 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 200 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day.

**[0171]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein wherein the subject is in the fed state. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein wherein the subject is in the fasted state.

**[0172]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

**[0173]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 4 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 3 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 2 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 1 hour before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 30 mins before sleep.

**[0174]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

**[0175]** In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 11 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 10 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 9 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 8 pm at night.

**[0176]** In some embodiments, the steroid or pharmaceutically acceptable salt thereof is a glucocorticoid or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid or a pharmaceutically acceptable salt there is prednisone, cortisone, prednisolone, triamcinolone, methylprednisolone, betamethasone, dexamethasone, hydrocortisone or a pharmaceutically acceptable salt thereof.

**[0177]** In some embodiments, the levels of A4 and ACTH in the subject are determined from a biological sample from the subject. In some embodiments, the biological sample is selected from the group of blood, blood fractions, plasma, serum, urine, other types of bodily secretions, and saliva. In some embodiments, the biological sample is obtained non-invasively.

**[0178]** In some embodiments, the subject is a pediatric patient. In some embodiments, the subject is from about 0 years old to about 18 years old. In some embodiments, the subject is an adult patient.

**[0179]** In some embodiments, the steroid and the CRF1 antagonist are administered concurrently. In some embodiments, the steroid and the CRF1 antagonist are administered in one pharmaceutical composition. In some embodiments, the steroid and the CRF1 antagonist are administered concurrently in separate pharmaceutical compositions. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially.

**[0180]** In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 24 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 8 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 2 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 10 minutes.

**[0181]** In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

**[0182]** In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the glucocorticoid is hydrocortisone.

**[0183]** In some embodiments, the glucocorticoid is hydrocortisone and the dose administered is less than the recommended dose of 15-25 mg/day.

**[0184]** In some embodiments, the glucocorticoid is prednisone and the dose administered is less than the recommended dose of 5-7.5 mg/day.

**[0185]** In some embodiments, the glucocorticoid is prednisolone and the dose administered is less than the recommended dose of 4-6 mg/day.

**[0186]** In some embodiments, the glucocorticoid is dexamethasone and the dose administered is less than the recommended dose of 0.25-0.5 mg/day.

## EXAMPLES

**[0187]** The following examples further illustrate the invention but should not be construed as in any way limiting its scope. In particular, the processing conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

**[0188]** All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed.

Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

**Example 1 – Identifying discrete subgroups of patients with CAH based on A4 and ACTH levels in a subject who has CAH**

**[0189]** Study Compound 3, a Phase 2, open-label, first-in-CAH-patients, proof-of-concept, dose ranging study, evaluated the safety and efficacy of repeated doses of SPR001 in adults with classic CAH. The population (n=24; with 2 subjects completing 2 cohorts) consisted of subjects with classic CAH that is not adequately controlled despite a stable glucocorticoid regimen based on the assessment of a single hormone at study screening, 17-OHP > 800 ng/dl, which is 4 times the upper limit of a normal reference range of 17-OHP level. 17-OHP was chosen as the hormone as an inclusion criterion, as at the time, it represented the state-of-art in CAH for assessment of disease severity and adequacy of glucocorticoid therapy. The study comprised 3 cohorts, Cohort A was a 6-week intra-subject dose escalation treatment period with three 2-week treatment periods of 200 mg glucocorticoid (QD) (only daily), 600 mg QD and 1000 mg QD without washout between treatment periods. Cohorts B and C consisted of 2-week treatment periods of either 100 bis in die (BID) (twice daily) (Cohort C) or 200 mg BID (Cohort B). At baseline, the following hormones were assessed, 17-OHP, ACTH and A4. The same hormones were assessed at the end of each 2-week treatment period.

**[0190]** The inclusion criterion of an elevated 17-OHP (>800 ng/dL) was expected, based on the current state-of-art, to enroll subjects with elevated ACTH, a precursor to 17-OHP, and elevated A4, a downstream androgen of 17-OHP. An elevated 17-OHP corresponded to both elevated and non-elevated pre (ACTH) and post (A4) stream hormones. This is evidenced in Table 1. All cohorts met the criteria of elevated 17-OHP as evidenced in the geometric means. Subjects in Cohort B, while having elevated 17-OHP, did not have elevated ACTH or elevated A4. Cohorts A and C had all 3 hormones elevated corresponding to the state-of-the-art.

*Table 1 – Cohorts assessed in a Phase 2, open-label, first-in-CAH-patients, proof-of-concept, dose ranging study*

| | **Cohort A Compound 3 200/600/1000 QD (N=10)** | **Cohort B Compound 3 200 BID (N=8)** | **Cohort C Compound 3 100 BID (N=7)** |
|---|---|---|---|
| **Screening 17-OHP, ng/dL** | | | |
| Geometric Mean (CV%) | 3887.3 (125.6) | 3157.8 (109.1) | 6106.8 (113.6) |
| **Baseline (8am) 17-OHP, ng/dL** | | | |
| Geometric Mean (CV%) | 7362.0 (95.2) | 1954.2 (344.2) | 6753.4 (96.0) |
| **Baseline (8 am)ACTH, pg/mL** | | | |

| | | | |
|---|---|---|---|
| Geometric Mean (CV%) | 306.72 (97.1) | 27.17 (190.6) | 292.45 (100.9) |
| **Baseline (8am) A4, ng/dL** | | | |
| Geometric Mean (CV%) | 286.9 (168.1) | 93.0 (194.6) | 242.2 (121.8) |

**[0191]** A clustering approach, supported and guided by clinical input, was used to define subgroups based on baseline hormone control of A4 and ACTH. The inclusion of 17-OHP as an input occluded the identification of clear subgroups which was non-obvious.

**[0192]** Three subgroups of patients were identified (see FIG.1):

- Subgroup One: Subjects with A4 and ACTH levels generally lower than two-fold the upper limit of normal for each laboratory assessment respectively.
- Subgroup Two: Subjects with A4 and ACTH generally higher than two-fold the upper limit of normal for each laboratory assessment respectively.
- Subgroup Three: Subjects with either A4 or ACTH above two fold and the other below two-fold the upper limit of normal for each laboratory assessment respectively.
- Subgroups 2 and 3 can be combined into a single subgroup.

**[0193]** By classifying the patients into subgroup types based on A4 and ACTH, it provides an alternative method to assessing diseases severity of subjects based on 17-OHP and A4. In addition, these subgroups provide a basis for different, yet sequential, methods of treatment.

**Example 2 –Phase 2 Clinical Studies**

**[0194]** A clinical study is conducted involving up to 52 weeks treatment of Compound 3 with concurrent daily glucocorticoid therapy for the treatment of adults with classic CAH. After screening using A4 and ACTH level criteria, eligible patients are enrolled into up to 12 weeks of placebo-controlled treatment followed by 40 weeks of open label treatment and a 4-week washout/safety follow-up period.

**[0195]** The population are composed of subjects from subgroup 2, approximately n=18 per treatment group and a range of doses between 50 mg to 200 mg and placebo. Each subject receives Compound 3 or placebo and a glucocorticoid daily for up to 12 weeks in a double-blind matter. Following the placebo-controlled period, all subjects receive open label compound 3 as various doses and a glucocorticoid will be administered as an oral daily dose as in the double-blind period. Patients self-administer Compound 3 for up to 52 weeks. The maximum treatment period for placebo is 12 weeks.

**[0196]** Study Design

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 2

- Interventional Study Model: double-blind, placebo controlled (12 weeks), open label (up to 40 weeks)
- Allocation: Equal Randomization
- Enrollment: Up to approximately 72

**Outcome Measures**

*Primary Outcome Measures:*

1. Assess reduction in key hormones such as ACTH, A4 and 17-OHP.

*Secondary Outcome Measures:*

2. Assess normalization proportions for key hormones such as ACTH, A4 and 17-OHP.

**Eligibility**

- Minimum Age: 16 Years
- Maximum Age: 65 Years
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

**Criteria:**

*Inclusion Criteria:*

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated A4 and ACTH more than two times the upper limit of normal laboratory reference range at screening and baseline
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

*Exclusion Criteria:*

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

**[0197]** The disclosed compound 3 is an inhibitor of the CYP3A4 pathway and dexamethasone (DEX) is primarily metabolized through the CYP3A4 pathway. As part of the study, pre and pose concentrations of DEX and cortisol were measured. In some embodiments, the biomarker reduction analysis comprises all subjects. In some embodiments, the biomarker reduction analysis does not comprise DEX-treated subjects.

**[0198]** As shown in FIGS. 2A and 2B, time matched changes among different treatment groups of ACTH level measured from 10 pm the day before to 8am the next day are illustrated in

non-dexamethasone subjects. A pooled baseline (dotted) and 2 lines (solid) representing two dose groups (doses = 200 mg and doses > 200 mg) using the percentage change from dose group baseline presented as percentage change from the pooled baseline. The figures are divided by disease control group, poor disease control with highly elevated ACTH and A4 and the good disease control group with ACTH and A4 that is near normal or below normal ranges. Each group has elevated 17-OHP.

**[0199]** According to FIG. 2A, in the poor disease group the geometric means post 4 am are highly elevated reaching values greater than 400 pg/mL or greater than 6 x upper limit of normal (ULN)(63.3 pg/mL). Treatment with compound 3 reduced the magnitude of the increase in ACTH post 3 am demonstrating an improvement in the serial hormone profile. According to FIG. 2B, in the good disease control group, the baseline serial profile was below the ULN throughout the evaluated time period. Treatment with compound 3 generally maintained the serial profile below the ULN. The observed changes are likely representative of intra-subject daily variation.

**[0200]** As shown in FIGS. 3A and 3B, the time matched changes among different treatment groups of 17-OHP level measured from 10 pm the day before to 8am the next day are illustrated in non-dexamethasone subjects . A pooled baseline (dotted) and 2 lines (solid) representing two dose groups (doses = 200 mg and doses > 200 mg) using the percentage change from dose group baseline presented as percentage change from the pooled baseline. The figures are divided by disease control group, poor disease control with highly elevated ACTH and A4 and the good disease control group with ACTH and A4 that is near normal or below normal ranges. In both groups, 17-OHP is elevated above its target (1200 ng/dL). The Y-axis is different with the poor disease control group exceeding 8000 ng/dL in FIG. 3A and the good disease group was near an upper bound of approximately 3000 ng/dL in FIG. 3B. In both groups, treatment with compound 3 reduced the magnitude of the increase in 17-OHP post 3 am demonstrating an improvement in the serial hormone profile.

**[0201]** As shown in FIGS. 4A and 4B, the time matched changes among different treatment groups of A4 level measured from 6 am to 8 am the same day in non-dexamethasone subjects. A pooled baseline (dotted) and 2 lines (solid) representing two dose groups (doses = 200 mg and doses > 200 mg) using the percentage change from dose group baseline presented as percentage change from the pooled baseline. The figures are divided by disease control group, poor disease control with highly elevated ACTH and A4 and the good disease control group with ACTH and A4 that is near normal or below normal ranges. Each group has elevated 17-OHP.

**[0202]** As shown in FIG. 4A, the baseline profile for the poor disease control group is above the blended gender based ULN of approximately 212 ng/dL. Treatment with compound 3 improves the A4 profile in subjects toward the blended gender based ULN of approximately 212

ng/dL. As shown in FIG. 4B, the baseline profile for the good disease control group is well below the blended gender based ULN of approximately 212 ng/dL. Treatment with compound 3 was able to further reduce A4 level compared to the baseline level. The small variation about the baseline likely representative of intra-subject daily variation.

**Example 3 – Phase 2 Clinical Studies.**

**[0203]** A Phase 2 Study is conducted involving a up to 52 weeks treatment multiple-dose study of Compound 3 and a glucocorticoid for the treatment of adults with classic CAH. After screening with the criteria disclosed herein, eligible patients are enrolled into up to 52 weeks of treatment followed by a 4-week washout/safety follow-up period.

**[0204]** The population are composed of subgroup one subjects, approximately n=30 with a dose of 200 mg and n=30 with placebo. Each subject receives Compound 3 or placebo and a glucocorticoid daily for up to 24 weeks in a double-blind manner. Compound 3 and a glucocorticoid are administered as an oral daily dose. Following the double-blind period, all subject will receive open label compound 3 at 200 mg. Patients self-administer Compound 3 for up to 52 weeks. After a minimum of 2 weeks of concomitant treatment of Compound 3 and a glucocorticoid, subjects are eligible for reductions in their glucocorticoid. Reduction occurs at 5 mg hydrocortisone equivalent increments over a period of 24 weeks with subjects eligible for up to 5 dose reductions prior to study end.

**[0205] Study Design**

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 2
- Interventional Study Model: double-blind (24 weeks) open-label (28 weeks)
- Allocation: Equal Randomization
- Enrollment: Up to approximately 60 [n=30 per group]

**Outcome Measures**

*Primary Outcome Measure:*

1. Reduction of glucocorticoid dose

*Secondary Outcome Measure:*

2. Assess normalization proportions for each key hormone
3. Assess impact of reductions of glucocorticoid dose on signs and symptoms of CAH
4. Assess impact of reductions of glucocorticoid dose on overall glucocorticoid toxicity Index.

**Eligibility**

- Minimum Age: 18 Years
- Maximum Age: 65
- Sex: All

- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

**Criteria:**

*Inclusion Criteria:*

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated A4 and ACTH <1.5x upper limit of normal at screening and baseline
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

*Exclusion Criteria:*

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

**[0206]** While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

## CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating Congenital Adrenal Hyperplasia (CAH), comprising administering a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof to a subject, wherein when said subject has a level of at least one steroid hormone that is less than two times an upper limit of a reference range of said at least one steroid hormone level , a dose of said steroid or a pharmaceutically acceptable salt thereof is reduced compared to a dose of said steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient that does not receive said $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein said subject has a level of a second and different steroid hormone that is less than two times an upper limit of a reference range of said second and different steroid hormone level.

3. The method of either claim 1 or claim 2, wherein said steroid hormone is selected from the group consisting of adrenocorticotropic hormone (ACTH), androstenedione (A4), 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, dehydroepiandrosterone, androstenediol, testosterone, dihydrotestosterone, estrone, estradiol, and estriol.

4. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than two times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than two times an upper limit of a reference range of ACTH.

5. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than two times an upper limit of a reference range of 17-OHP and a level of A4 that is less than two times an upper limit of a reference range of A4.

6. The method of one of claims 1-3, wherein said subject has a level of A4 that is less than two times an upper limit of a reference range of A4 and a level of ACTH that is less than two times an upper limit of a reference range of ACTH.

7. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.75 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.75 times an upper limit of a reference range of ACTH.

8. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.75 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.75 times an upper limit of a reference range of A4.

9. The method of one of claims 1-3, wherein said subject has a level of A4 that is less than 1.75 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.75 times an upper limit of a reference range of ACTH.

10. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.5 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.5 times an upper limit of a reference range of ACTH.

11. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.5 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.5 times an upper limit of a reference range of A4.

12. The method of one of claims 1-3, wherein said subject has a level of A4 that is less than 1.5 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.5 times an upper limit of a reference range of ACTH.

13. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.25 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.25 times an upper limit of a reference range of ACTH.

14. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.25 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.25 times an upper limit of a reference range of A4.

15. The method of one of claims 1-3, wherein said subject has a level of A4 that is less than 1.25 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.25 times an upper limit of a reference range of ACTH.

16. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than one times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than one times an upper limit of a reference range of ACTH.

17. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than one times an upper limit of a reference range of 17-OHP and a level of A4 that is less than one times an upper limit of a reference range of A4.

18. The method of one of claims 1-3, wherein said subject has a level of A4 that is less than one times an upper limit of a reference range of A4 and a level of ACTH that is less than one times an upper limit of a reference range of ACTH.

19. The method of any of claims 1-18, further comprising reducing said dose of said steroid or a pharmaceutically acceptable salt thereof in a 5 mg increment.

20. A method of treating Congenital Adrenal Hyperplasia (CAH), comprising administering a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof to a subject, wherein when said

subject has a level of at least one steroid hormone that is more than an upper limit of a reference range of said at least one steroid hormone level, a dose of said steroid or a pharmaceutically acceptable salt thereof is not reduced compared to a dose of said steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient that does not receive said CRF1 antagonist or a pharmaceutically acceptable salt thereof.

21. The method of claim 20, wherein said subject has a level of said at least one steroid hormone that is more than two times an upper limit of a reference range of said at least one steroid hormone level.

22. The method of claim 20, wherein said subject has a level of said at least one steroid hormone that is more than 1.75 times an upper limit of a reference range of said at least one steroid hormone level.

23. The method of claim 20, wherein said subject has a level of said at least one steroid hormone that is more than 1.5 times an upper limit of a reference range of said at least one steroid hormone level.

24. The method of claim 20, wherein said subject has a level of said at least one steroid hormone that is more than 1.25 times an upper limit of a reference range of said at least one steroid hormone level.

25. The method of claim 20, wherein said steroid hormone is selected from the group consisting of adrenocorticotropic hormone (ACTH), androstenedione (A4), 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, dehydroepiandrosterone, androstenediol, testosterone, dihydrotestosterone, estrone, estradiol, and estriol.

26. The method of any of claims 20-25, further comprising maintaining said dose of said steroid or a pharmaceutically acceptable salt thereof until said levels of at least two steroid hormones are less than 2 times said upper limit of said reference ranges of said two steroid hormones respectively.

27. The method of any of claims 20-25, further comprising reducing said dose of said steroid or a pharmaceutically acceptable salt thereof in a 5 mg increment when said levels of at least two steroid hormones are less than 2 times said upper limit of said reference ranges of said two steroid hormones respectively.

28. The method of claim 27, wherein said at least two steroid hormones comprise 17-OHP and ACTH.

29. The method of claim 27, wherein said at least two steroid hormones comprise 17-OHP and A4.

30. The method of claim 27, wherein said at least two steroid hormones comprise A4 and ACTH.

31. The method of any of claims 1-30, wherein said reference range of ACTH or A4 level of said subject is controlled by a factor selected from the group consisting of age, sex, menopausal status, laboratory setting, time of a day and combinations thereof.

32. The method of any of claims 1-30, wherein said level of ACTH or A4 is 2 times, 1.5 times, 1.25 times, or 1 times said upper limit of said normal range of ACTH or A4 level of said subject.

33. The method of any of claims 1-30, wherein said amount of said steroid or a pharmaceutically acceptable salt thereof comprises a range of about 10 mg to about 80 mg of hydrocortisone equivalents, wherein said steroid or a pharmaceutically acceptable salt thereof is administered daily.

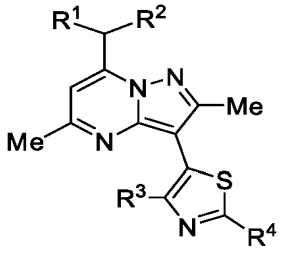
34. The method of any of claims 1-30, wherein said amount of said $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof comprises a range of about 10 mg to about 200 mg, wherein said $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof is administered daily.

35. The method of any of claims 1-34, wherein said subject is treated for a period of about 4 weeks to about 36 weeks.

36. The method of any of claims 1-34, wherein after said subject is treated for a period of about 4 weeks to about 36 weeks, said subject is reassessed to determine if a different method of treating CAH should be administered.

37. The method of any one of claims 1-36, wherein said $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003.

38. The method of any one of claims 1-37, wherein said $CRF_1$ antagonist is a compound of Formula (I):

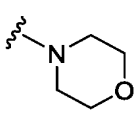
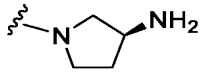
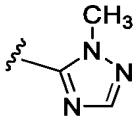
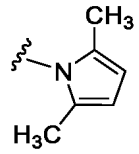



(I),

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ and $R^2$ are independently ethyl or *n*-propyl;

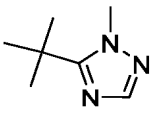
$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

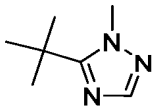
$R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and

$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

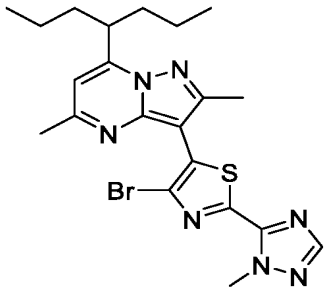
39. The method of claim 38, wherein $R^3$ is Cl, Br, methyl, or trifluoromethyl.

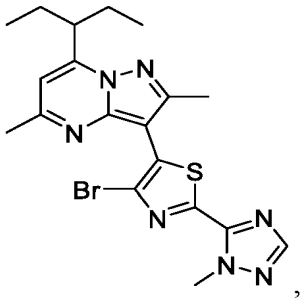
40. The method of claims 38 or 39, wherein $R^3$ is Cl, Br, or methyl.

41. The method of any one of claims 38-40, wherein $R^4$ is Br, $R^aR^bN$–, pyridin-4-yl, morpholin-4-yl, or .

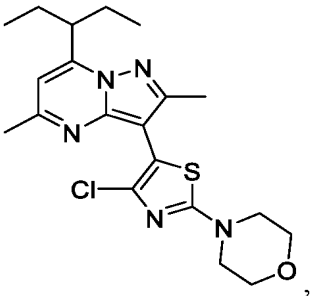
42. The method of any one of claims 38-40, wherein $R^4$ is morpholin-4-yl or .

43. The method of any one of claims 38-40, wherein $R^4$ is hydrogen, Br, $R^aR^bN$– and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

44. The method of claim 38, wherein the compound is , or a pharmaceutically acceptable salt thereof.

45. The method of claim 38, wherein the compound is , or a pharmaceutically acceptable salt thereof.

46. The method of claim 38, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

47. The method of any one of claims 1-46, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg to about 200 mg total daily dose to the subject.

48. The method of any one of claims 1-46, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

49. The method of any one of claims 1-46, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject.

50. The method of any one of claims 1-46, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject.

51. The method of any one of claims 1-46, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 75 mg total daily dose to the subject.

52. The method of any one of claims 1-46, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject.

53. The method of any one of claims 1-46, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject.

54. The method of any one of claims 1-46, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is in the form of microparticles.

55. The method of claim 54, wherein the average size of the microparticles is between about 1 μm to about 20 μm.

56. The method of claim 54, wherein the average size of the microparticles is between about 5 μm to about 15 μm.

57. The method of claim 54, wherein the average size of the microparticles is less than about 10 μm.

58. The method of any one of claims 1-56, wherein the CRF1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

59. The method of any one of claims 1-56, wherein the steroid or a pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

60. The method of claim 58 or 59, wherein the pharmaceutical composition is in the form of a capsule or a tablet.

61. The method of claim 60, wherein the capsule is a hard gelatin capsule.

62. The method of claim 60, wherein the capsule is a soft gelatin capsule.

63. The method of any one of claims 60-62, wherein the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

64. The method of any one of claims 58-63, wherein the pharmaceutical composition is free of additional excipients.

65. The method of any one of claims 58-63, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

66. The method of claim 60, wherein the pharmaceutical composition is in the form of a tablet.

67. The method of claim 66, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

68. The method of any one of claims 1-66, wherein the steroid or pharmaceutically acceptable salt thereof is a glucocorticoid or a pharmaceutically acceptable salt thereof.

69. The method of claim 68, wherein the glucocorticoid or a pharmaceutically acceptable salt thereof is prednisone, cortisone, prednisolone, triamcinolone, methylprednisolone, betamethasone, dexamethasone, hydrocortisone or a pharmaceutically acceptable salt thereof.

70. The method of any one of claims 1-69, wherein levels of steroid hormones in the subject are determined from a biological sample from the subject.

71. The method of claim 70, wherein the biological sample is selected from the group of blood, blood fractions, plasma, serum, and saliva.

72. The method of claim 70, wherein the biological sample is obtained non-invasively.

73. The method of any one of claims 1-72, wherein said subject is tested in the morning.

74. The method of any one of claims 1-72, wherein said subject is tested to determine morning levels of A4 and ACTH.

75. The method of any one of claims 1-72, wherein the subject is a pediatric patient.

76. The method of any one of claims 1-72, wherein the subject is from about 0 years old to about 18 years old.

77. The method of any one of claims 1-72, wherein the subject is an adult patient.

78. The method of any one of claims 1-77, wherein the steroid and the $CRF_1$ antagonist are administered concurrently.

79. The method of any one of claims 1-77, wherein the steroid and the $CRF_1$ antagonist are administered in one pharmaceutical composition.

80. The method of any one of claims 1-77, wherein the steroid and the $CRF_1$ antagonist are administered concurrently in separate pharmaceutical compositions.

81. The method of any one of claims 1-77, wherein the steroid and the $CRF_1$ antagonist are administered sequentially.

82. The method of claim 81, wherein the steroid and the $CRF_1$ antagonist are administered sequentially within 24 hours.

83. The method of claim 81, wherein the steroid and the $CRF_1$ antagonist are administered sequentially within 8 hours.

84. The method of claim 81, wherein the steroid and the $CRF_1$ antagonist are administered sequentially within 2 hours.

85. The method of claim 81, wherein the steroid and the $CRF_1$ antagonist are administered sequentially within 10 minutes.

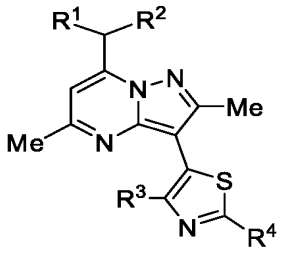
86. The method of any one of claims 1-85, wherein CAH is classic CAH.

87. The method of any one of claims 1-85, wherein CAH is non-classic CAH.

88. A composition comprises a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof, wherein said $CRF_1$ antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003.

89. The composition of claim 88, wherein said a steroid or a pharmaceutically acceptable salt thereof is exogenous glucocorticoids (GC) or a pharmaceutically acceptable salt thereof.

90. The composition of either claim 88 or 89, wherein said $CRF_1$ antagonist is a compound of Formula (I):

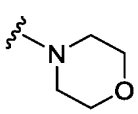
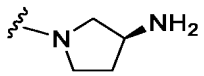
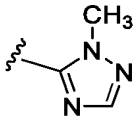
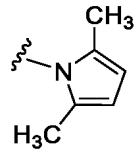


(I),

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ and $R^2$ are independently ethyl or *n*-propyl;

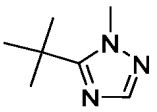
$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

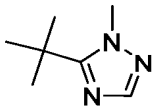
$R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ; and

$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

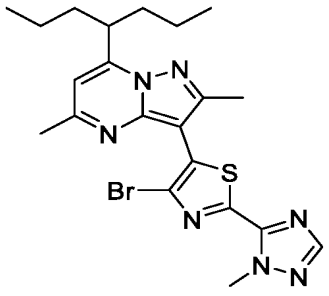
91. The composition of claim 90, wherein $R^3$ is Cl, Br, methyl, or trifluoromethyl.

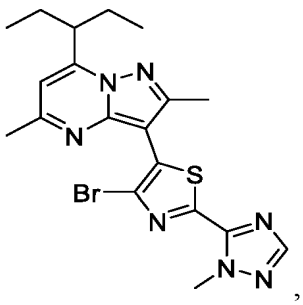
92. The composition of claims 90 or 91, wherein $R^3$ is Cl, Br, or methyl.

93. The composition of any one of claims 90-92, wherein $R^4$ is Br, $R^aR^bN$–, pyridin-4-yl, morpholin-4-yl, or .

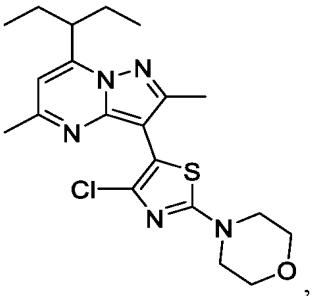
94. The composition of any one of claims 90-92, wherein $R^4$ is morpholin-4-yl or .

95. The composition of any one of claims 90-92, wherein $R^4$ is hydrogen, Br, $R^aR^bN$– and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

96. The composition of claim 90, wherein the compound is , or a pharmaceutically acceptable salt thereof.

97. The composition of claim 90, wherein the compound is , or a pharmaceutically acceptable salt thereof.

98. The composition of claim 90, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

99. The composition of any one of claims 90-98, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg to about 200 mg total daily dose to the subject.

100. The composition of any one of claims 90-98, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

101. The composition of any one of claims 90-98, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject.

102. The composition of any one of claims 90-98, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject.

103. The composition of any one of claims 90-98, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 75 mg total daily dose to the subject.

104. The composition of any one of claims 90-98, wherein the $CRF_1$ antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject.

105. The composition of any one of claims 90-98, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject.

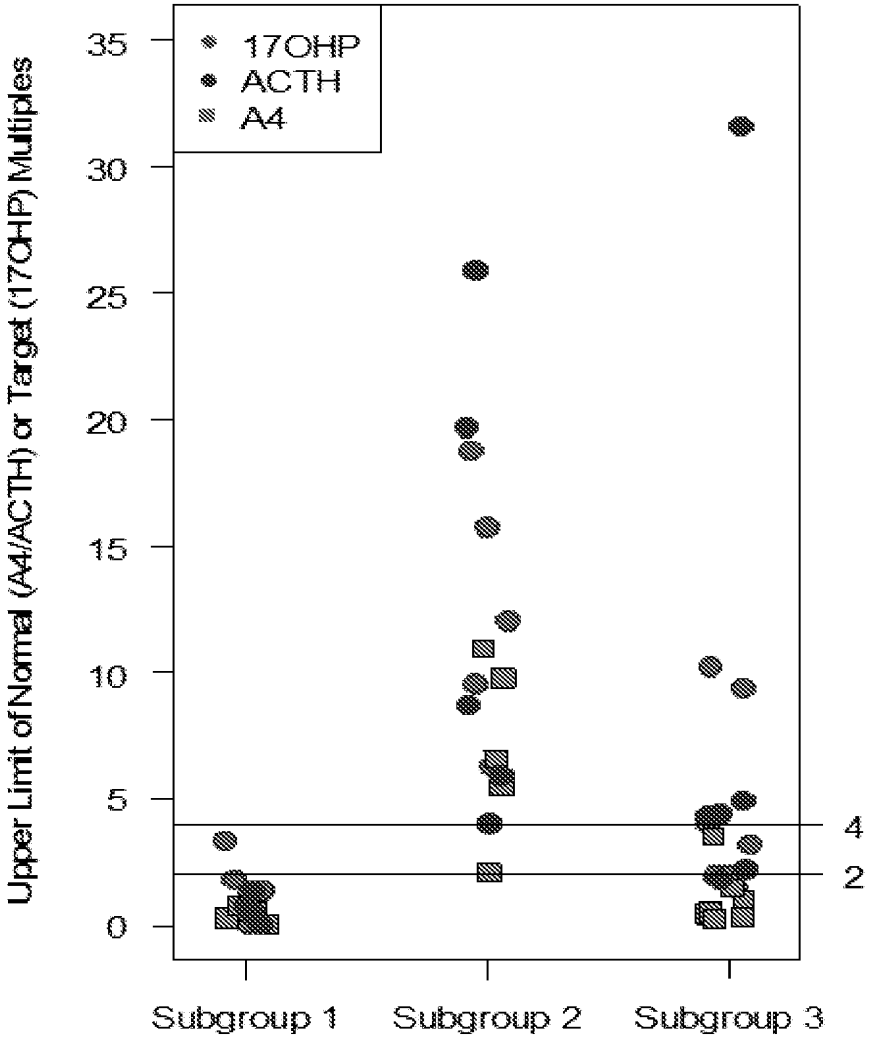

17OHP
ACTH
A4
Upper Limit of Normal (A4/ACTH) or Target (17OHP) Multiples
35
30
25
20
15
10
5
0
4
2
Subgroup 1
Subgroup 2
Subgroup 3

*FIG. 1*

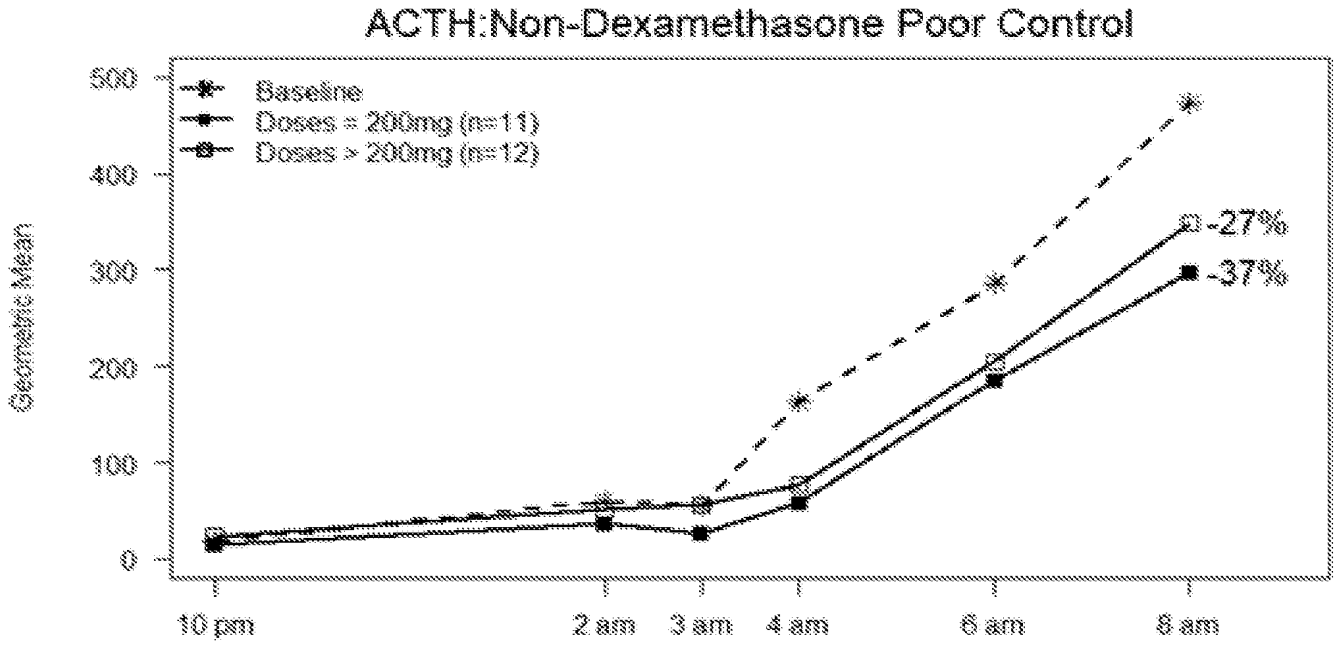

ACTH:Non-Dexamethasone Poor Control
Baseline
Doses = 200mg (n=11)
Doses > 200mg (n=12)
Geometric Mean
500
400
300
200
100
0
-27%
-37%
10 pm
2 am
3 am
4 am
6 am
8 am

FIG. 2A

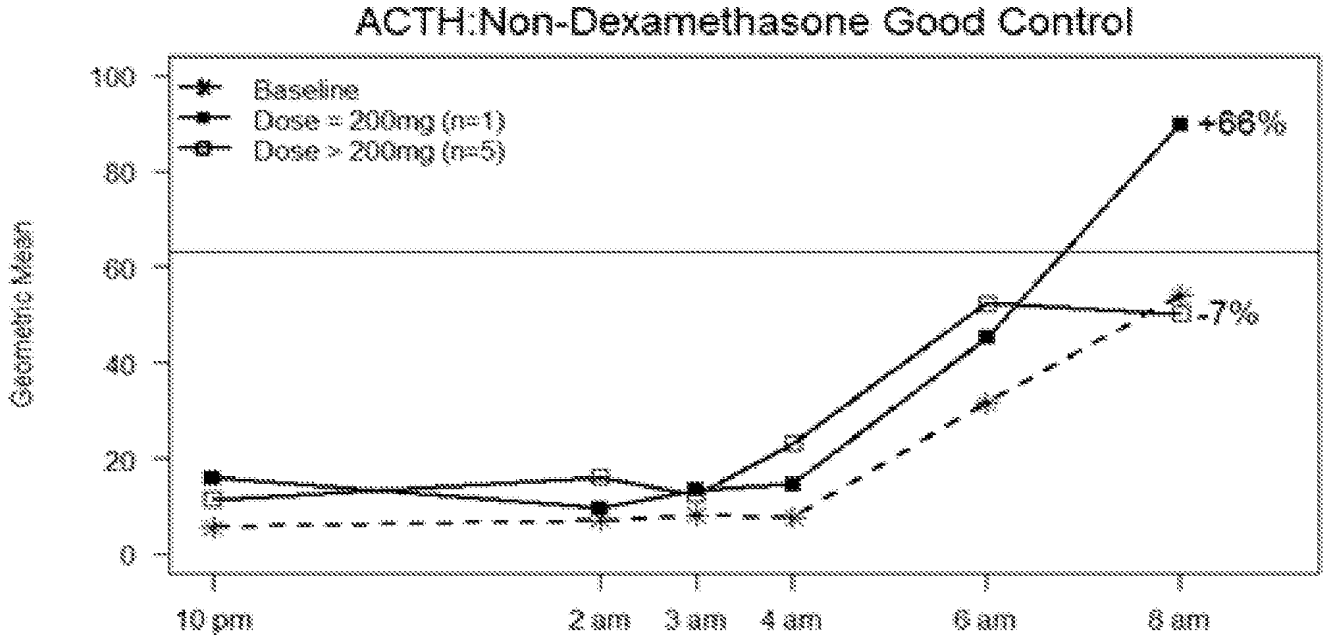

ACTH:Non-Dexamethasone Good Control
Baseline
Dose = 200mg (n=1)
Dose > 200mg (n=5)
Geometric Mean
100
80
60
40
20
0
+66%
-7%
10 pm
2 am
3 am
4 am
6 am
8 am

FIG. 2B

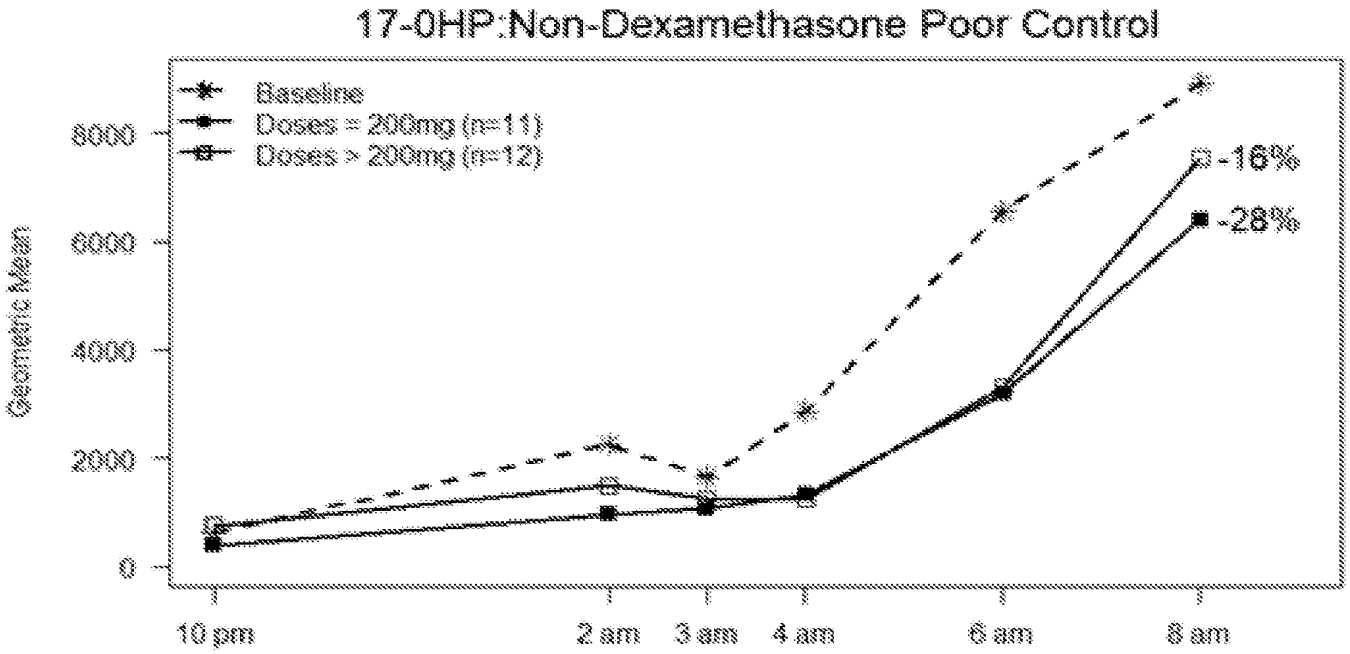

17-0HP:Non-Dexamethasone Poor Control
Baseline
Doses = 200mg (n=11)
Doses > 200mg (n=12)
Geometric Mean
8000
6000
4000
2000
0
10 pm
2 am
3 am
4 am
6 am
8 am
-16%
-28%

FIG. 3A

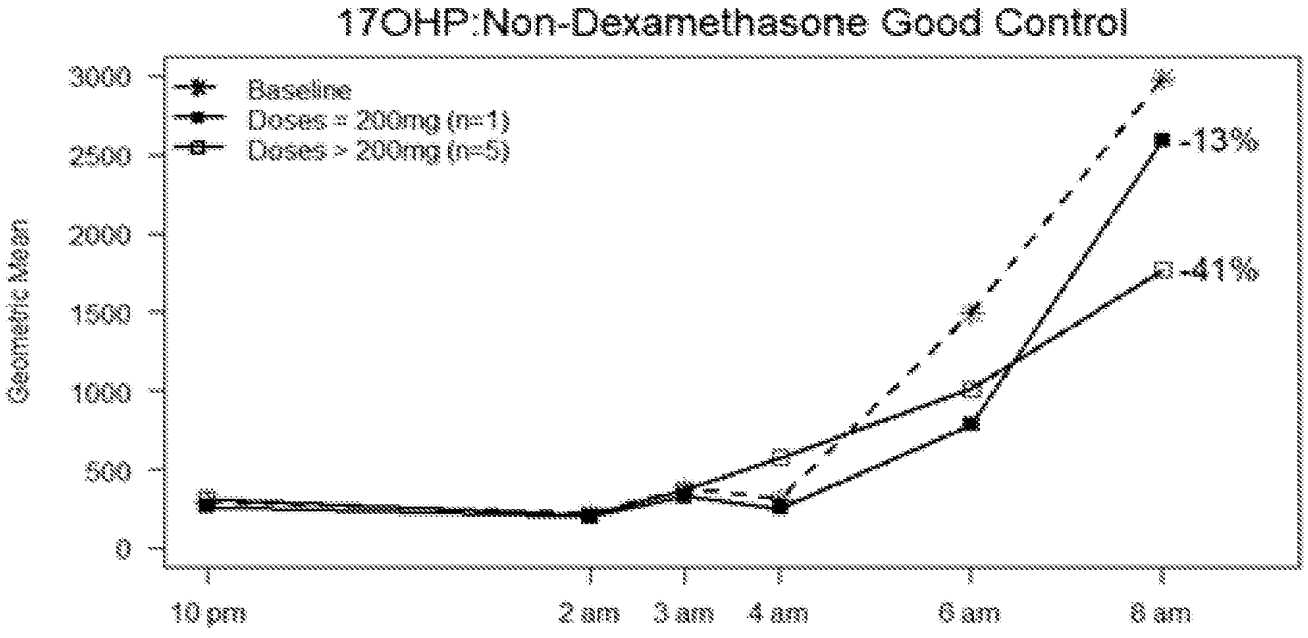

17OHP:Non-Dexamethasone Good Control
Baseline
Doses = 200mg (n=1)
Doses > 200mg (n=5)
Geometric Mean
3000
2500
2000
1500
1000
500
0
10 pm
2 am
3 am
4 am
6 am
8 am
-13%
-41%

FIG. 3B

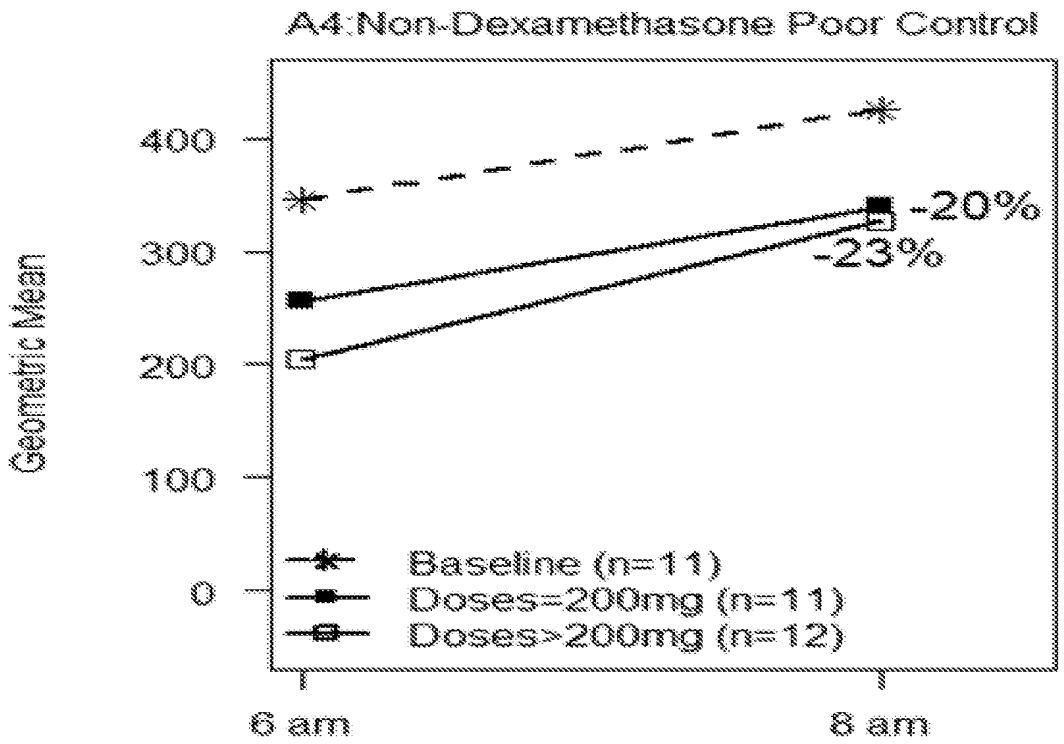

A4:Non-Dexamethasone Poor Control
Geometric Mean
400
300
200
100
0
-20%
-23%
Baseline (n=11)
Doses=200mg (n=11)
Doses>200mg (n=12)
6 am
8 am

FIG. 4A

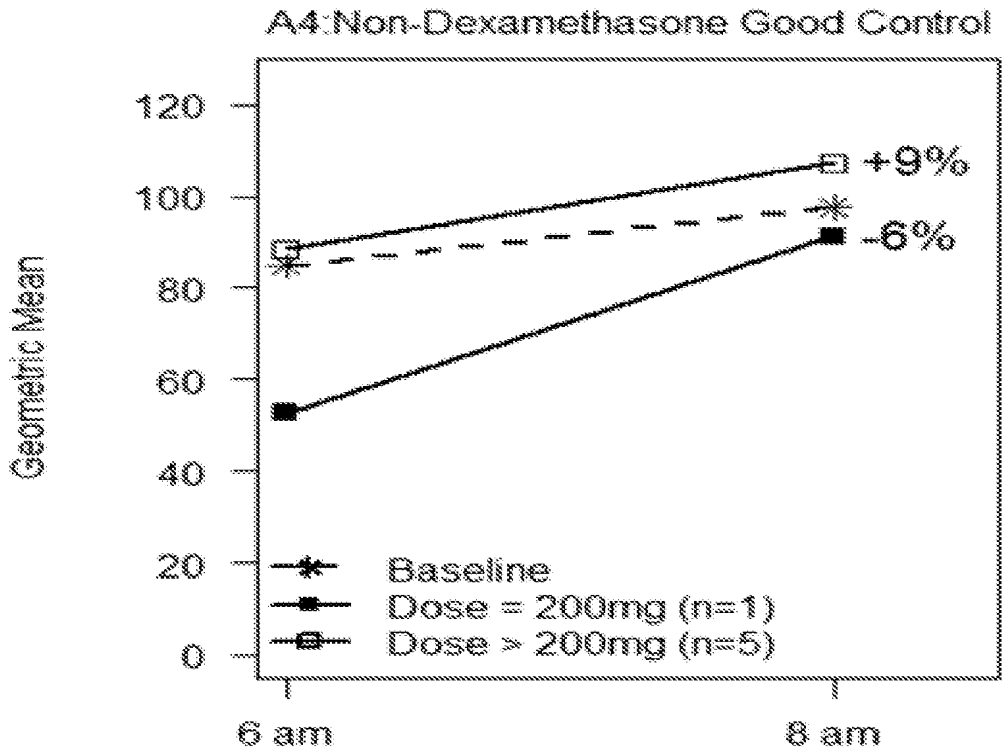

A4:Non-Dexamethasone Good Control
Geometric Mean
120
100
80
60
40
20
0
+9%
-6%
Baseline
Dose = 200mg (n=1)
Dose > 200mg (n=5)
6 am
8 am

FIG. 4B

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/US2020/042820**

**A. CLASSIFICATION OF SUBJECT MATTER**

**A61K 31/56(2006.01)i, A61K 31/57(2006.01)i, A61K 38/22(2006.01)i, A61K 31/519(2006.01)i, A61K 31/5377(2006.01)i, A61P 5/38(2006.01)i, C07D 487/04(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/56; A61K ; A61K 31/4412; A61K 31/4545; A61K 31/519; A61P 25/24; A61K 31/57; A61K 38/22; A61K 31/5377; A61P 5/38; C07D 487/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & keywords: Congenital Adrenal Hyperplasia (CAH), corticortropin-releasing factor type-1 (CRF1) antagonist

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2017-0020877 A1 (NEUROCRINE BIOSCIENCES, INC.) 26 January 2017<br>claims 14-18; TABLE 2; paragraphs [0054], [0070], [0086] | 88-91,96-98 |
| X | WO 2005-020910 A2 (PHARMACIA CORPORATION) 10 March 2005<br>claims 1-5 | 88-91,96-98 |
| A | US 2011-0136865 A1 (BUNTINX, E.) 09 June 2011<br>the whole document | 88-91,96-98 |
| A | WO 2013-160317 A2 (HOLSBOERMASCHMEYER NEUROCHEMIE GMBH) 31 October 2013<br>the whole document | 88-91,96-98 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 November 2020 (24.11.2020) | **25 November 2020 (25.11.2020)** |

| Name and mailing address of the ISA/KR | Authorized officer |
|---|---|
| International Application Division<br>Korean Intellectual Property Office<br>189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea | Jung, Da Won |
| Facsimile No. +82-42-481-8578 | Telephone No. +82-42-481-5373 |

Form PCT/ISA/210 (second sheet) (July 2019)

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2020/042820**

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 2017-0020877 A1 | 26/01/2017 | CN 106102740 A | 09/11/2016 |
| | | CN 111228274 A | 05/06/2020 |
| | | EP 3096756 A1 | 30/11/2016 |
| | | JP 2017-503030 A | 26/01/2017 |
| | | JP 2019-081814 A | 30/05/2019 |
| | | JP 6585625 B2 | 02/10/2019 |
| | | KR 10-2016-0106176 A | 09/09/2016 |
| | | US 2019-0231781 A1 | 01/08/2019 |
| | | WO 2015-112642 A1 | 30/07/2015 |
| WO 2005-020910 A2 | 10/03/2005 | US 2005-0085479 A1 | 21/04/2005 |
| | | WO 2005-020910 A3 | 09/06/2005 |
| US 2011-0136865 A1 | 09/06/2011 | EP 1708790 A1 | 11/10/2006 |
| | | EP 1708790 B1 | 21/04/2010 |
| | | EP 2272514 A1 | 12/01/2011 |
| | | US 2007-0078162 A1 | 05/04/2007 |
| | | US 2011-0207776 A1 | 25/08/2011 |
| | | US 8304431 B2 | 06/11/2012 |
| | | WO 2005-053796 A1 | 16/06/2005 |
| WO 2013-160317 A2 | 31/10/2013 | EP 2841068 A2 | 04/03/2015 |
| | | EP 2841068 B1 | 28/11/2018 |
| | | JP 2015-516979 A | 18/06/2015 |
| | | US 2015-0094310 A1 | 02/04/2015 |
| | | WO 2013-160317 A3 | 03/01/2014 |

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/US2020/042820**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-87
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-87 pertain to methods for treatment of the human body and thus relate to a subject-matter which this International Searching Authority is not required to search under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv).

2. ☒ Claims Nos.: 39,44-46,55-57,61,62,66,67,69,71,72,82-85
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 39,44-46,55-57,61,62,66,67,69,71,72,82-85 are regarded to be unclear because they refer to claims 38,54,60,66,68,70,81, which does not comply with PCT Rule 6.4(a).

3. ☒ Claims Nos.: 4-19,31-38,40-43,47-54,58-60,63-65,68,70,73-81,86,87,92-95,99-105
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 May 2023 (25.05.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/091684 A1

(51) International Patent Classification:
*C07D 487/04* (2006.01) *A61P 5/38* (2006.01)
*A61K 31/5377* (2006.01) *A61P 15/08* (2006.01)
*A61K 47/12* (2006.01) *A61P 5/24* (2006.01)
*A61K 9/00* (2006.01)

(21) International Application Number:
PCT/US2022/050436

(22) International Filing Date:
18 November 2022 (18.11.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/281,462 19 November 2021 (19.11.2021) US
63/340,874 11 May 2022 (11.05.2022) US

(71) Applicant: **SPRUCE BIOSCIENCES, INC.** [US/US]; 611 Gateway Boulevard, Suite 740, South San Francisco, California 94080 (US).

(72) Inventors: **REDDY, Dasharatha**; 611 Gateway Boulevard, Suite 740, South San Francisco, California 94080 (US). **RAJAGOPAL, Ashokraj**; 611 Gateway Boulevard, Suite 740, South San Francisco, California 94080 (US). **WANG, Lu**; 611 Gateway Boulevard, Suite 740, South San Francisco, California 94080 (US). **BARNES, Christopher**; 611 Gateway Boulevard, Suite 740, South San Francisco, California 94080 (US).

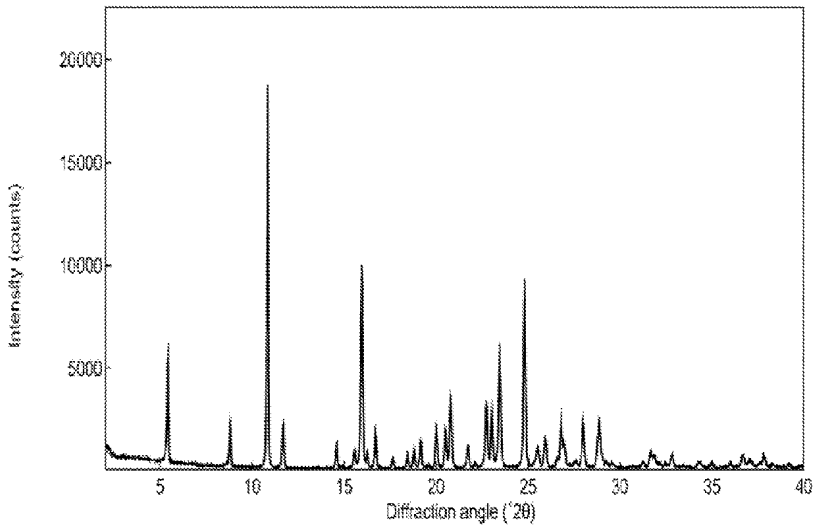
(74) Agent: **OLSHEMSKI, Stephen**; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, California 94304 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,

(54) Title: CRYSTALLINE COMPOSITION OF TILDACERFONT AND METHODS OF USE AND PREPARATION THEREOF

FIG. 1




(57) Abstract: Described herein are crystalline composition, methods of making such crystalline composition, pharmaceutical compositions and medicaments comprising such crystalline composition, and methods of using such crystalline composition in the treatment of conditions, diseases, or disorders that would benefit from modulation of Corticotropin-releasing hormone receptor 1 (CRF1).

[Continued on next page]

WO 2023/091684 A1

LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Published:**

— *with international search report (Art. 21(3))*

# CRYSTALLINE COMPOSITION OF TILDACERFONT AND METHODS OF USE AND PREPARATION THEREOF

## CROSS-REFERENCE

**[0001]** This application claims the benefit of U.S. Provisional Application No. 63/281,462 filed November 19, 2021 and U.S. Provisional Application No. 63/340,874 filed May 11, 2022, each of which is incorporated herein by reference in its entirety.

## INCORPORATION BY REFERENCE

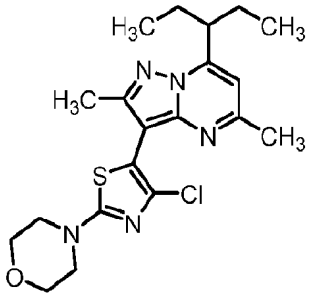
**[0002]** All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

## BACKGROUND

**[0003]** Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

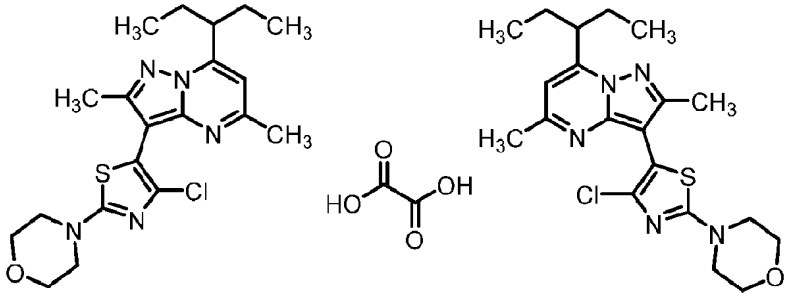
## SUMMARY

**[0004]** In a first aspect, the present disclosure provides a crystalline composition comprising Compound I:




Compound I.

**[0005]** In some embodiments, the crystalline composition comprising Compound 1 comprises a crystalline composition comprising Formula I:



Formula I.

**[0006]** In some embodiments, the crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I) have unit cell parameters at T = 150°K of: a = 34.003(4) Å, b = 6.5843(13) Å, c = 21.062(5) Å; β = 108.703(12)°, V = 4466.5(15) $Å^3$ and a monoclinic C2/c space group.

**[0007]** In some embodiments, the crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I) is characterized by:

(a) an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å;

(b) an X-ray powder diffraction pattern substantially the same as shown in FIG. 1;

(c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C;

(d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C;

(e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2;

(f) a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C;

(g) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3; or

(h) combinations thereof.

**[0008]** In some embodiments, the crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I) is characterized by (a), (c), (d), and (f).

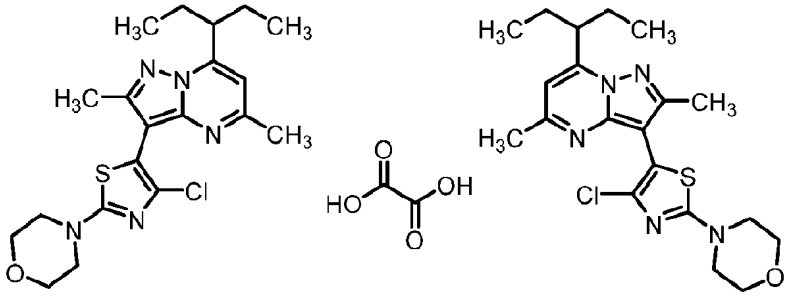
**[0009]** In some embodiments, the composition comprising a CRF1 antagonist (e.g., a crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by an X-ray powder diffraction pattern comprising one or more peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the CRF1 antagonist (e.g., crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from 5.44 ± 0.2° 2-θ, 20.78 ± 0.2° 2-θ, 22.74 ± 0.2° 2-θ, 23.04 ± 0.2° 2-θ, 26.80 ± 0.2° 2-θ, and 28.86 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least five peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the crystalline composition is characterized by an X-ray powder diffraction pattern substantially the same as shown in FIG. 1.

**[0010]** In some embodiments, the crystalline composition comprising a CRF1 antagonist (e.g., crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C. In some embodiments, the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset from about 160 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset from about 150 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset from about 160 °C to about 180 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset at about 160 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising a peak of about 166 °C. In some embodiments, the crystalline composition is

characterized by a DSC thermogram comprising a peak from about 166 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 166 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 160 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 150 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 160 °C to about 180 °C. In some embodiments, the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2.

**[0011]** In some embodiments, the crystalline composition comprising a CRF1 antagonist (e.g., crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3. In some embodiments, the crystalline composition is characterized by a TGA thermogram comprising a loss in mass of more than 10% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a TGA thermogram comprising a loss in mass of less than about 15% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a TGA thermogram comprising a loss in mass of less than about 20% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a dynamic vapor sorption (DVS) trace substantially the same as shown in FIG. 4.

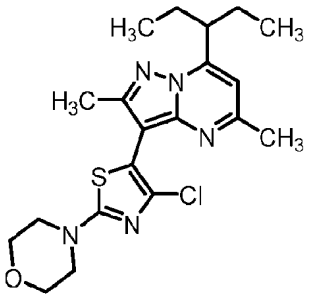
**[0012]** In some aspects, the present disclosure provides a pharmaceutical composition comprising crystalline composition comprising Formula I:



Formula I,

and at least one pharmaceutically acceptable carrier or excipient.

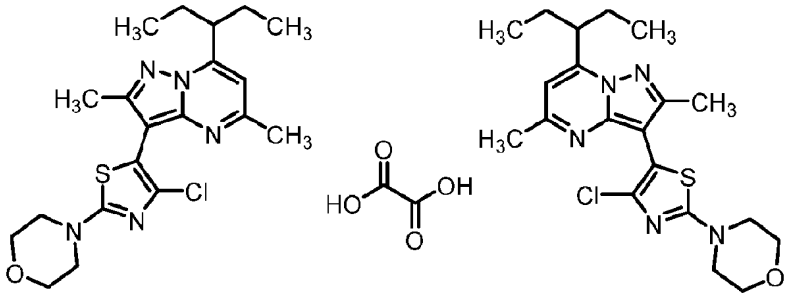
**[0013]** In some aspects, the present disclosure provides a pharmaceutical composition comprising Compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition comprising Compound 1 is a crystalline pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises crystalline Compound 1.

**[0014]** In another aspect, the present disclosure provides a method of preparing a crystalline composition comprising Compound 1 (e.g., comprising Formula I:



Formula I,

wherein the method comprises:

a) dissolving 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) and oxalic acid in a solvent;

(b) heating the solution or slurry from step (a); and

(c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0015]** In some embodiments of the method of preparing the crystalline composition comprising Compound I (e.g., comprising Formula I), the solvent in step (a) comprises acetone, heptane, water, 2-butanol, ethyl acetate, 2-propanol, methyl tert-butyl ether, ethanol, methyl ethyl ketone, 1-pentanol, or a combination thereof. In some embodiments, the solvent in step (a) is heptane. In some embodiments, the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone. In some embodiments, the solvent in step (a) is a mixture of heptane and methyl ethyl ketone. In some embodiments, step (b) is heated at about 50 °C.

**[0016]** In another aspect, the present disclosure provides a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the subject has congenital adrenal hyperplasia (CAH).

**[0017]** In another aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the CAH is a classic CAH. In some embodiments, the CAH is a non-classical CAH.

**[0018]** In another aspect, the present disclosure provides a method of improving (e.g., lessening the severity and/or frequency) hyperandrogenic symptoms in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism, amenorrhea, and alopecia.

**[0019]** In another aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

**[0020]** In another aspect, the present disclosure provides a method of improving (e.g., lessening the severity and/or frequency) metabolic symptoms in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the metabolic symptoms are

selected from the group consisting of body weight, BMI, fat mass, waist circumference, blood pressure and glycemic control. Metabolic symptoms may be evaluated using an assessment, such as, for example, fasting lipid panel, homeostatic model assessment of insulin resistance [HOMA-IR] based on fasting glucose and insulin levels, glycated hemoglobin [HbAlc], glucose tolerance test.

**[0021]** In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

**[0022]** In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

**[0023]** In another aspect, the present disclosure provides a method of treating endometriosis or improving the symptoms of endometriosis in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition improves the symptom of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition reduces the symptoms of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition prevents or lowers the perception of pain experienced by the subject (e.g., as measured on a pain scale). In some embodiments, the administration of the crystalline composition or the pharmaceutical composition eliminates the perception of pain experienced by the subject.

**[0024]** In various embodiments of the methods as described herein, the crystalline composition or the pharmaceutical composition is administered at a dose from about 5

mg/day to about 1000 mg/day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fed state. A fed state may mean that the subject has eaten within a 30-minute period before of receiving the crystalline composition or the pharmaceutical compositions. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fasted state. A fasted state may mean that the subject has not eaten within a 30-minute period before of receiving the crystalline composition or the pharmaceutical compositions. In some embodiments, the crystalline composition or the pharmaceutical composition is administered at least once per day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered once a day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered twice a day.

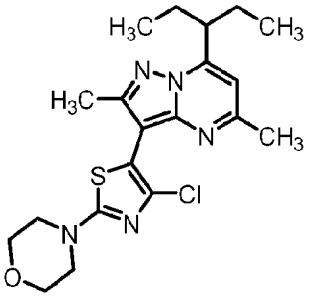
**[0025]** In various embodiments of the methods as described herein, the method further comprises administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen agent. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone. In some embodiments, the additional therapeutic agent is a different CRF1 antagonist.

**[0026]** In various embodiments of the methods as described herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, or the pharmaceutical composition comprising the crystalline composition as described herein. In some embodiments, the additional therapy is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, the pharmaceutical composition comprising the crystalline composition as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

**[0027]** In various embodiments of the methods, the subject is from about 9 years of age to about 18 years of age. In some embodiments, the subject is from about 8 years of age to about 55 years of age.

**[0028]** In additional aspects, provided herein is a pharmaceutical composition comprising a CRF1 antagonist, wherein the composition is characterized by an X-ray powder diffraction

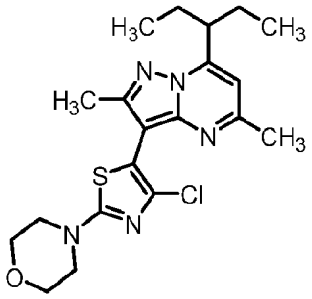
pattern comprising a peak selected from any one or more of 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the composition is characterized by X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from 5.44 ± 0.2° 2-θ, 20.78 ± 0.2° 2-θ, 22.74 ± 0.2° 2-θ, 23.04 ± 0.2° 2-θ, 26.80 ± 0.2° 2-θ, and 28.86 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least five peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the CRF1 antagonist comprises Compound 1:




Compound 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is a crystalline pharmaceutical composition. In some embodiments, the crystalline pharmaceutical composition further comprises oxalic acid. In some embodiments, the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1.

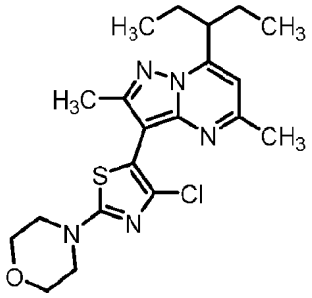
**[0029]** In additional aspects, provided herein is a pharmaceutical composition comprising a CRF1 antagonist, wherein the pharmaceutical com-position is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C. In some embodiments, the pharmaceutical composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset

of about 164 °C and a peak of about 166 °C. In some embodiments, the pharmaceutical composition is characterized by a melting point of about 166 °C. In some embodiments, the CRF1 antagonist comprises Compound 1:



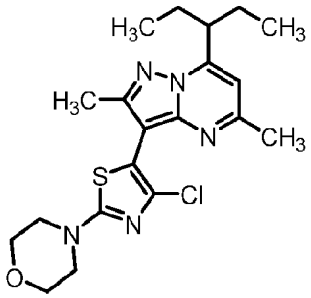
**[0030]** Compound 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is a crystalline pharmaceutical composition. In some embodiments, the crystalline pharmaceutical composition further comprises oxalic acid. In some embodiments, the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1. In some embodiments, the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C.

**[0031]** In additional aspects, provided herein is method of preparing a crystalline composition comprising Compound 1:



Compound 1, wherein the method comprises: (a) dissolving Compound 1 and an acid in a solvent; (b) heating the solution or slurry from step (a); and (c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound 1. In some embodiments, the acid comprises oxalic acid. In some embodiments, the solvent in step (a) is heptane. In some embodiments, the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone. In some embodiments, the solvent in step (a) is a mixture of heptane and methyl ethyl ketone. In some embodiments, step (b) is heated at about 50 °C.

**[0032]** In additional aspects, further provided herein is a pharmaceutical composition comprising Compound 1:



Compound 1, or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is present in an amount of 25% w/w; and a diluent in about 5% to about 70% In some embodiments, Compound 1 is in an amount of about 50 mg to about 200 mg. In some embodiments, Compound 1 is in an amount of about 50 mg. In some embodiments, wherein the diluent is selected from the group consisting of calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose monohydrate, and a combination thereof. In some embodiments, the diluent is lactose monohydrate. In some embodiments, the lactose monohydrate is about 20% to about 45% by weight of the pharmaceutical composition. In some embodiments, the lactose monohydrate is about 20% to about 40.25% by weight of the pharmaceutical composition. In some embodiments, the lactose monohydrate is in an amount that is about 16.1, 40.25, 80.5, or 322 mg. In some embodiments, the diluent is microcrystalline cellulose. In some embodiments, the pharmaceutical composition further comprises a second diluent, wherein the second diluent comprises microcrystalline cellulose. In some embodiments, the microcrystalline cellulose is about 25% by weight of the pharmaceutical composition. In some embodiments, the microcrystalline cellulose is in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition further comprises a binder, wherein the binder is selected from the group consisting of corn starch and potato starch, gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC), and a combination thereof. In some embodiments, the binder comprises HPC. In some embodiments, the HPC is about 3% by weight of the solid dosage form. In some embodiments, the pharmaceutical composition further comprises a surfactant, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate, tetradecyl trimethyl ammonium bromide with dodecyl, hexadecyl compound, benzalkonium chloride, cetylpyridinium chloride, alkylsulphate, alkylethoxylate sulphate, soap, carxylate ion, sulfate

ion, sulfonate ion, polyoxyethylene derivative, polyoxypropylene derivative, polyol derivative, polyol ester, polyoxyethylene ester, poloxamers, glocol, glycerol ester, sorbitan derivative, and polyethylene glycol, and a combination thereof. In some embodiments, the surfactant comprises sodium lauryl sulfate. In some embodiments, the sodium lauryl sulfate is about 0.75% by weight of the solid dosage form. In some embodiments, the sodium lauryl sulfate is in an amount that is about 1.5 mg. In some embodiments, the pharmaceutical composition further comprises a disintegrant, wherein the disintegrant is selected from the group consisting of starch, alginic acid, ac-di-sol, croscarmellose sodium, sodium starch glycolate, and crospovidone, and a combination thereof. In some embodiments, the disintegrant comprises croscarmellose sodium.

**[0033]** In some embodiments, the pharmaceutical composition further comprises a glidant, wherein the glidant comprises colloidal silicon dioxide. In some embodiments, the colloidal silicon dioxide is about 1% by weight of the solid dosage form. In some embodiments, the colloidal silicon dioxide is in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition further comprises a lubricant, wherein the lubricant is selected from the group consisting of talc, stearic acid, magnesium stearate, sodium stearyl fumarate, and a combination thereof. In some embodiments, the pharmaceutical formulation is in a solid dosage form. In some embodiments, the solid dosage form is a tablet. In some embodiments, the solid dosage form is a granules form. In some embodiments, said granules form is packaged in a capsule. In some embodiments, said granules form is packaged in a sachet.

**[0034]** In additional aspects, provided herein is a pharmaceutical formulation, comprising: (a) about 10 mg to about 300 mg of 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-α) pyrimidine (Compound 1), or a pharmaceutically acceptable salt or solvate thereof; (b) a first diluent in about 40% to about 45% by weight, wherein the first diluent comprises lactose monohydrate; (c) a second diluent in about 25% by weight, wherein the second diluent comprises microcrystalline cellulose; (d) about 1% to about 6% by weight of hydroxypropyl cellulose; (e) about 0.5% to about 5% by weight of sodium lauryl sulfate; and (f) about 4% by weight of croscarmellose sodium.

## DESCRIPTION OF THE DRAWINGS

**[0035]** The novel features of the present disclosure are set forth with particularity in the appended claims. An understanding of the features and advantages of the present disclosure may be obtained by reference to the following detailed description that sets forth illustrative

embodiments, in which the principles of the present disclosure are utilized, and the accompanying drawings of which:

**[0036] FIG. 1** shows the X-ray powder diffraction (XRPD) pattern for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0037] FIG. 2** shows the differential scanning calorimetry (DSC) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0038] FIG. 3** shows the thermogravimetric analysis (TGA) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0039] FIG. 4** shows the dynamic vapor sorption (DVS) trace for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0040] FIG. 5** shows the infrared (IR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0041] FIG. 6** shows the proton nuclear magnetic resonance ($^1$H NMR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0042] FIG. 7** shows the Raman spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

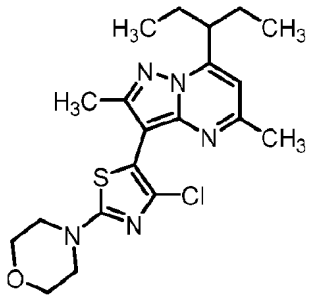
## DETAILED DESCRIPTION

**[0043]** 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) is a potent antagonist of Corticotropin-releasing hormone receptor 1 (CRF1). CRF1 antagonists may be useful in the treatment of various diseases, conditions, and disorders for which abnormal CRF1 activity plays a role.

**[0044]** Crystalline forms of a small molecule drug candidate, such as a CRF1 antagonist, may have different physical properties, including melting point, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties may have an effect on the ability to process or manufacture a drug substance and the drug product. Moreover, differences in these properties can and often lead to different pharmacokinetics profiles for different polymorphic forms of a drug. Polymorphism may affect the quality, safety, and/or efficacy of a drug product, such as a CRF1 antagonist. Thus, there still remains a need for crystalline compositions of CRF1 antagonist. The present disclosure addresses this need and provides related advantages as well.

**Compound 1**

**[0045]** As described herein, Compound 1 refers to 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine, which has the chemical structure as shown below:



Compound 1.

**[0046]** Compound 1 is a CRF1 modulator. CRF1 modulator, such as a CRF1 antagonist or inhibitor, are useful in the treatment of various conditions and disorders that are mediated by CRF1 activities.

**[0047]** In some embodiments, the present disclosure provides a crystalline composition comprising Compound 1. In some embodiments, the crystalline composition comprises Compound 1 and a weak acid (e.g., oxalic acid) (e.g., in a molar ratio of 2:1). In some embodiments, the crystalline composition comprises Compound 1 and an acid in a molar ratio of 2:1. In some embodiments, the crystalline composition comprises Compound 1 and an acid in a molar ratio of 1:1.

**[0048]** As used herein, "crystalline," "crystalline form," "polymorph," "Form," and "form" may be used interchangeably herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, co-crystals, polymorphs, pseudopolymorphs, salts, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. Compounds of the present disclosure include crystalline and amorphous forms of those compounds, including, for example, polymorphs, co-crystals, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

**[0049]** As used herein, "co-crystal" may be used to describe crystalline compositions comprising multi-component crystals based on hydrogen bonding interactions of hydrogen ions to form salt forms. In some embodiments, the crystalline composition as described

herein are co-crystals comprising an acid (e.g., a weak acid (e.g., oxalic acid)) and Compound 1.

**Definitions**

**[0050]** A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative, such as those known in the art, for example, described in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

**[0051]** As used herein, "treating" and like terms refer to reducing the severity and/or frequency of symptoms, eliminating symptoms and/or the underlying cause of said symptoms, reducing the frequency or likelihood of symptoms and/or their underlying cause, delaying, preventing and/or slowing the progression of diseases and/or disorders and improving or remediating damage caused, directly or indirectly, by the diseases and/or disorders.

**[0052]** As used herein, "delaying development of a disease" or the like, means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease (such as cancer) or a sign or symptom of the disease. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease. For example, a late stage cancer, such as development of metastasis, may be delayed.

**[0053]** As used herein, an "effective dosage" or "effective amount" of drug, compound, or pharmaceutical composition is an amount sufficient to effect beneficial or desired results. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, delaying development of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. In the case of cancer or tumor, an effective amount of the drug may have the effect in reducing the number of cancer cells;

reducing the tumor size; inhibiting (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibiting, to some extent, tumor growth; and/or relieving to some extent one or more of the symptoms associated with the disorder. An effective dosage can be administered in one or more administrations. For purposes of this invention, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an "effective dosage" may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

**[0054]** As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. Inhibition may refer to reduction of a disease or symptoms of disease. Inhibition may refer to a reduction in the activity of a particular protein or nucleic acid target. The protein may be deoxycytidine kinase. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein.

**[0055]** The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule.

**[0056]** The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, a modulator of a target protein changes by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. A modulator of a disease decreases a symptom, cause, or characteristic of the targeted disease.

**[0057]** "Selective" or "selectivity" or the like of a compound refers to the compound's ability to discriminate between molecular targets.

**[0058]** "Specific", "specifically", "specificity", or the like of a compound refers to the compound's ability to cause a particular action, such as inhibition, to a particular molecular target with minimal or no action to other proteins in the cell.

**[0059]** "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

**[0060]** The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

**[0061]** As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc.

**[0062]** By "co-administer" it is meant that a compound described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example, an anticancer agent as described herein. The compounds described

herein can be administered alone or can be co-administered to the patient. Co-administration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. anticancer agents).

**[0063]** Co-administration includes administering one active agent (e.g. Compound 1 described herein) within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent (e.g. anti-cancer agents). Also contemplated herein, are embodiments, where co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. Co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In some embodiments, the active and/or adjunctive agents are linked or conjugated to one another. In some embodiments, the compounds described herein are combined with treatments for cancer such as chemotherapy or radiation therapy.

**[0064]** The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease means that the disease is caused by (in whole or in part), a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function, or a side-effect of the compound (e.g. toxicity) is caused by (in whole or in part) the substance or substance activity or function.

**[0065]** "Patient," "subject," "patient in need thereof," and "subject in need thereof" are herein used interchangeably and refer to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human. A "cancer-patient" is a patient suffering from, or prone to developing cancer.

**[0066]** Unless clearly indicated otherwise, the term "individual" as used herein refers to a mammal, including but not limited to, bovine, horse, feline, rabbit, canine, rodent, or primate (e.g., human). In some embodiments, an individual is a human. In some embodiments, an individual is a non-human primate such as chimpanzees and other apes and monkey species. In some embodiments, an individual is a farm animal such as cattle, horses, sheep, goats and swine; pets such as rabbits, dogs and cats; laboratory animals including rodents, such as rats,

mice, and guinea pigs; and the like. In some embodiments, the invention find use in both human medicine and in the veterinary context.

**[0067]** "Disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. In some embodiments, the disease as used herein refers to cancer.

**[0068]** As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly indicates otherwise.

**[0069]** The term "about" when used in reference to numerical ranges, cut-offs, or specific values is used to indicate that the recited values may vary by up to as much as 10% from the listed value. As many of the numerical values used herein are experimentally determined, it should be understood by those skilled in the art that such determinations can, and often times will, vary among different experiments. The values used herein should not be considered unduly limiting by virtue of this inherent variation. Thus, the term "about" is used to encompass variations of ±10% or less, variations of ±5% or less, variations of ±1% or less, variations of ±0.5% or less, or variations of ±0.1% or less from the specified value.

**[0070]** It is understood that aspect and variations of the invention described herein include "consisting" and/or "consisting essentially of" aspects and variations.

**Crystalline Composition Comprising Compound I (e.g., Comprising Formula I)**

**[0071]** The crystalline composition prepared according to the methods of the present disclosure may be characterized by any methodology comprising the art. For example, the crystalline composition comprising Compound 1 ((e.g., comprising Formula I) e.g., prepared comprising the methods of the present disclosure)) may be characterized by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and/or spectroscopy (e.g., Raman, solid state nuclear magnetic resonance (ssNMR), proton nuclear magnetic resonance ($^1$H NMR), and infrared (IR)). In some embodiments, crystallinity of the solid form is determined by X-Ray Powder Diffraction (XPRD).

**[0072]** Formula 1 may represent a composition comprising two molecules of Compound 1 and one molecules of oxalic acid. As such, Formula I may represent a molar ratio of Compound 1 to oxalic acid in a ratio of about 2:1.

**[0073]** XRPD: Crystalline composition according to the present disclosure may be characterized by XRPD (e.g., crystalline composition(s) comprising the present disclosure can also be identified by its characteristic XRPD peaks, such as show in FIG. 1). The relative intensities of XRPD peaks may vary, depending upon the particle size, the sample

preparation technique, the sample mounting procedure and the particular instrument employed. Moreover, instrument variation and other factors may affect the 2-θ values. Therefore, the XRPD peak assignments may vary, for example by plus or minus about 0.2 degrees.

**[0074]** DSC: Crystalline composition according to the present disclosure can also be identified by its characteristic DSC thermograms such as shown in FIG. 2. For DSC, it is known that the temperatures observed may depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms may vary, for example by plus or minus about 4°C.

**[0075]** TGA: Crystalline composition according to the present disclosure may also give rise to thermal behavior different from that of the amorphous material or other crystalline forms. Thermal behavior may be measured in the laboratory by thermogravimetric analysis (TGA) which may be used to distinguish some crystalline forms from others. In one aspect, the crystalline composition as described herein may be characterized by thermogravimetric analysis.

**[0076]** DVS: Crystalline composition comprising the present disclosure may also give rise to vapors sorption behavior different from that of the amorphous material or other crystalline forms. The vapor sorption behavior may be measured in the laboratory by dynamic vapor sorption (DVS) which may be used to distinguish some crystalline forms from others. In one aspect, the crystalline composition as described herein may be characterized by dynamic vapor sorption.

**[0077]** The crystalline composition comprising Compound 1 (e.g. comprising Formula I) may be useful in the production of medicinal preparations and can be obtained by means of a crystallization process to produce crystalline and semi-crystalline forms or a solidification process to obtain the amorphous form. In some embodiments, the crystallization is carried out by either generating the desired compound (for example Compound 1) in a reaction mixture and isolating the desired crystalline composition from the reaction mixture, or by dissolving raw compound (e.g., Compound 1) in a solvent, optionally with heat, followed by crystallizing/solidifying the product by cooling (including active cooling) and/or by the addition of an antisolvent for a period of time. The crystallization or solidification may be followed by drying carried out under controlled conditions until the desired water content is reached in the end crystalline composition.

**[0078] FIG. 1** shows the X-ray powder diffraction (XRPD) pattern for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0079] FIG. 2** shows the differential scanning calorimetry (DSC) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0080] FIG. 3** shows the thermogravimetric analysis (TGA) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

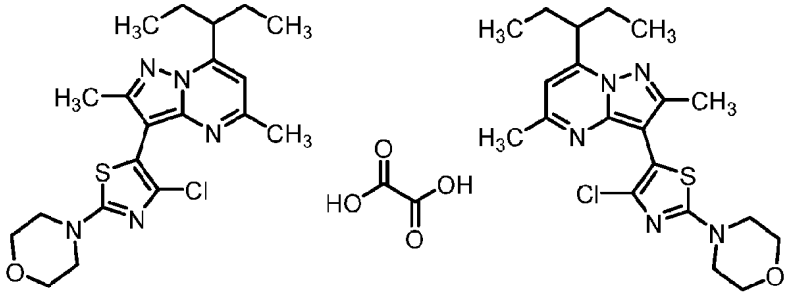
**[0081] FIG. 4** shows the dynamic vapor sorption (DVS) trace for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0082] FIG. 5** shows the infrared (IR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0083] FIG. 6** shows the proton nuclear magnetic resonance ($^1$H NMR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0084] FIG. 7** shows the Raman spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[0085]** In some aspects, the present disclosure provides a crystalline composition comprising Compound 1. In some embodiments the crystalline composition comprising Compound 1 is a crystalline composition comprising Formula I:



Formula I.

**[0086]** In some embodiments, Formula I represents Compound 1 and oxalic acid in a molar ratio of 2:1.

**[0087]** In some embodiments, the crystals of the crystalline composition comprising Compound 1 (e.g., comprising Formula I) has unit cell parameters at T = 150°K of: a = 34.003(4) Å, b = 6.5843(13) Å, c = 21.062(5) Å; β = 108.703(12)°, V = 4466.5(15) Å$^3$ and a monoclinic C2/c space group.

**[0088]** In some embodiments, the crystals of a composition (e.g., a crystalline composition comprising Compound 1 (e.g., comprising Formula I)) is characterized by:

(a) an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å;

(b) an X-ray powder diffraction pattern substantially the same as shown in FIG. 1;

(c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C;

(d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C;

(e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2;

(f) a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C;

(g) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3; or

(h) combinations thereof.

**[0089]** In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., v Formula I)) is characterized by an X-ray powder diffraction pattern comprising any one or more peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the XRPD pattern comprises at least one of the aforementioned peaks (10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å). In some embodiments, the XRPD pattern comprises at least two of the aforementioned peaks. In some embodiments, the XRPD pattern comprises at least three of the aforementioned peaks. In some embodiments, the XRPD pattern comprises at least four of the aforementioned peaks. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I) is characterized by an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.1° 2-θ, 15.96 ± 0.1° 2-θ, 23.44 ± 0.1° 2-θ, and 24.80 ± 0.1° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I) is characterized by an X-ray powder diffraction pattern comprising peaks at about 10.84° 2-θ, about 15.96° 2-θ, about 23.44° 2-θ, and about 24.80° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

**[0090]** In some embodiments, the X-ray powder diffraction (XRPD) pattern further comprising at least one peak selected from 5.44 ± 0.2° 2-θ, 20.78 ± 0.2° 2-θ, 22.74 ± 0.2° 2-θ, 23.04 ± 0.2° 2-θ, 26.80 ± 0.2° 2-θ, and 28.86 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from 5.44 ± 0.1° 2-θ, 20.78 ± 0.1° 2-θ, 22.74 ± 0.1° 2-θ, 23.04 ± 0.1° 2-θ, 26.80 ± 0.1° 2-θ, and 28.86 ± 0.1° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from about 5.44° 2-θ, about 20.78° 2-θ, about 22.74° 2-θ, about 23.04° 2-θ, about 26.80° 2-θ, and about 28.86° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

**[0091]** In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least two peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least three peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least four peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least five peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2°

2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least six peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least seven peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least eight peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks selected from 8.82 ± 0.1° 2-θ, 11.70 ± 0.1° 2-θ, 14.60 ± 0.1° 2-θ, 15.56 ± 0.1° 2-θ, 16.70 ± 0.1° 2-θ, 18.82 ± 0.1° 2-θ, 19.18 ± 0.1° 2-θ, 20.02 ± 0.1° 2-θ, 20.50 ± 0.1° 2-θ, 21.72 ± 0.1° 2-θ, 25.52 ± 0.1° 2-θ, 25.92 ± 0.1° 2-θ, 26.94 ± 0.1° 2-θ, and 28.00 ± 0.1° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks selected from 8.82° 2-θ, 11.70° 2-θ, 14.60° 2-θ, 15.56° 2-θ, 16.70° 2-θ, 18.82° 2-θ, 19.18° 2-θ, 20.02° 2-θ, 20.50° 2-θ, 21.72° 2-θ, 25.52° 2-θ, 25.92° 2-θ, 26.94° 2-θ, and 28.00° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

**[0092]** In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C. In some embodiments, the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 166 °C. In some embodiments, the

crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2.

**[0093]** In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 160 °C to about 170 °C, about 160 °C to about 169 °C, about 160 °C to about 168 °C, about 160 °C to about 167 °C, about 160 °C to about 166 °C, about 160 °C to about 165 °C, about 160 °C to about 164 °C, about 160 °C to about 163 °C, about 160 °C to about 162 °C, about 160 °C to about 161 °C, about 161 °C to about 170 °C, about 162 °C to about 170 °C, about 163 °C to about 170 °C, about 164 °C to about 170 °C, about 165 °C to about 170 °C, about 166 °C to about 170 °C, about 167 °C to about 170 °C, about 168 °C to about 170 °C, or about 169 °C to about 170 °C. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 162 °C to about 166 °C, for example at about 162 °C, about 163 °C, about 164 °C, 165 °C, or 166 °C. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., (e.g., comprising Compound 1))) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 164 °C. In some embodiments, the crystalline composition according for Formula I has a melting point of about 166 °C.

**[0094]** In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition decomposes above a temperature of about 50 °C, about 100 °C, about 150 °C, about 200 °C, about 250 °C, about 300 °C, about 350 °C, or about 400 °C. In some embodiments, the crystalline composition decomposes above a temperature of about 200 °C. In some embodiments, the crystalline composition decomposes above a temperature of about 250 °C. In some embodiments, the crystalline composition is characterized by a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3.

**[0095]** In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a dynamic vapor sorption (DVS) trace substantially the same as shown in FIG. 4.

**[0096]** In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is anhydrous.

**[0097]** In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is stable at room temperature. In some examples, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) can be stored at room temperature for an extended period of time without significant chemical degradation or change in the crystalline form. In some examples, crystalline composition comprising Compound 1 (e.g., comprising Formula I) can be stored at room temperature for a timer period of at least about 10 days, 30 days, 60 days, 90 days, 120 days, 150 days, or 180 days. In some examples, the crystalline composition can be stored at room temperature for a time period of more than about 180 days. In some examples, the crystalline composition can be stored at room temperature for a time period of 10-14 days, 10-18 days, 10-22 days, 10-26 days, 10-30 days, 10-40 days, 10-50 days, 10-60 days, 10-90 days, 10-120 days, 10-150 days, 10-180 days, 14-18 days, 14-22 days, 14-26 days, 14-30 days, 14-40 days, 14-50 days, 14-60 days, 14-90 days, 14-120 days, 14-150 days, 14-180 days, 18-22 days, 18-26 days, 18-30 days, 18-40 days, 18-50 days, 18-60 days, 18-90 days, 18-120 days, 18-150 days, 18-180 days, 22-26 days, 22-30 days, 22-40 days, 22-50 days, 22-60 days, 22-90 days, 22-120 days, 22-150 days, 22-180 days, 26-30 days, 26-40 days, 26-50 days, 26- 60 days, 26-90 days, 26-120 days, 26-150 days, 26-180 days, 30-40 days, 30-50 days, 30-60 days, 30-90 days, 30-120 days, 30-150 days, 30-180 days, 40-50 days, 40-60 days, 40-90 days, 40-120 days, 40-150 days, 40-180 days, 50-60 days, 50-90 days, 50-120 days, 50-150 days, 50-180 days, 60-90 days, 60-120 days, 60-150 days, 60-180 days, 90-120 days, 90-150 days, or 90-180 days. In some examples, the crystalline composition can be stored at room temperature for a time period of at least 10 days, 14 days, 18 days, 22 days, 26 days, 30 days, 40 days, 50 days, 60 days, 90 days, 120 days, 150 days, or 180 days.

**[0098]** In some embodiments, the crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) is stable at room temperature or temperatures above the room temperature and/or at high relative humidity (RH) (e.g., accelerated aging conditions or long-term storage conditions). In some embodiments, the crystalline composition is stable for at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, at least twelve months, at least fourteen months, at least sixteen months, and at least eighteen months. In some examples, the crystalline composition can be stored at about 25 °C and at about 75%

RH for an extended period of time without significant chemical degradation or change in the crystalline form. In some examples, the crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) can be stored at about 25 °C and at about 75% RH for a time period of at least about 10 days, 30 days, 60 days, 90 days, 120 days, 150 days, or 180 days. In some examples, the crystalline composition can be stored at about 25 °C and at about 75% RH for a time period of 10-14 days, 10-18 days, 10-22 days, 10-26 days, 10-30 days, 10-40 days, 10-50 days, 10-60 days, 10-90 days, 10-120 days, 10-150 days, 10-180 days, 14-18 days, 14-22 days, 14-26 days, 14-30 days, 14-40 days, 14-50 days, 14-60 days, 14-90 days, 14-120 days, 14-150 days, 14-180 days, 18-22 days, 18-26 days, 18-30 days, 18-40 days, 18-50 days, 18-60 days, 18-90 days, 18-120 days, 18-150 days, 18-180 days, 22-26 days, 22-30 days, 22-40 days, 22-50 days, 22-60 days, 22-90 days, 22-120 days, 22-150 days, 22-180 days, 26-30 days, 26-40 days, 26-50 days, 26- 60 days, 26-90 days, 26-120 days, 26-150 days, 26-180 days, 30-40 days, 30-50 days, 30-60 days, 30-90 days, 30-120 days, 30-150 days, 30-180 days, 40-50 days, 40-60 days, 40-90 days, 40-120 days, 40-150 days, 40-180 days, 50-60 days, 50-90 days, 50-120 days, 50-150 days, 50-180 days, 60-90 days, 60-120 days, 60-150 days, 60-180 days, 90-120 days, 90-150 days, or 90-180 days. In some examples, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) can be stored at about 25 °C for a time period of at least 10 days, 14 days, 18 days, 22 days, 26 days, 30 days, 40 days, 50 days, 60 days, 90 days, 120 days, 150 days, or 180 days.

**[0099]** In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is thermodynamically stable.

**[00100]** In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is highly bioavailable.

**[00101]** In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is stable under accelerated storage conditions.

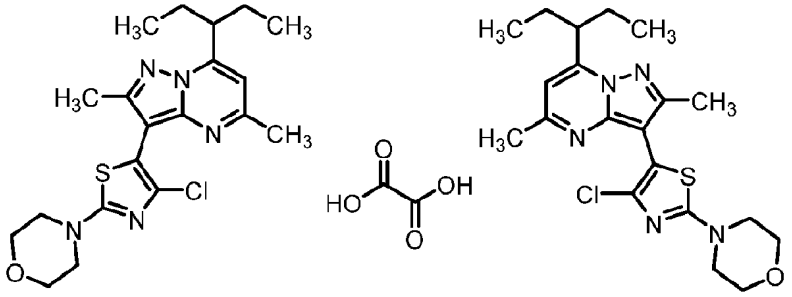
**[00102]** In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is characterized by an infrared (IR) spectrum substantially the same as shown in FIG. 5.

**[00103]** In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is characterized by a proton nuclear magnetic resonance ($^1$H NMR) spectrum substantially the same as shown in FIG. 6.

**[00104]** In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is characterized by a Raman spectrum substantially the same as shown in FIG. 7.

**Compositions and Formulations**

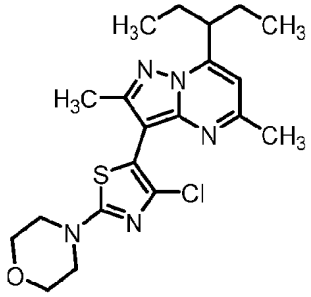
**[00105]** In some aspects, the present disclosure provides a pharmaceutical composition comprising a crystalline composition comprising Formula I:



Formula I,

and at least one pharmaceutically acceptable carrier or excipient.

**[00106]** In some aspects, the present disclosure provides a pharmaceutical composition comprising Compound 1:



Compound 1,

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition is a crystalline pharmaceutical composition comprising Compound 1. In some embodiments, the crystalline pharmaceutical composition comprising Compound 1 comprises Formula I.

***Dosage Form***

**[00107]** In some embodiments, the pharmaceutical composition described herein is provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of the crystalline composition comprising Compound 1 (e.g., comprising Formula I)

that is suitable for administration to a subject in a single dose. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

**[00108]** In some embodiments, the pharmaceutical compositions described herein are formulated as oral dosage forms. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules. In some embodiments, the pharmaceutical composition comprises one or more additional pharmaceutically acceptable excipients. See, e.g., Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005) for a list of pharmaceutically acceptable excipients.

*Capsule*

**[00109]** In some embodiments, the pharmaceutical composition comprising the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is formulated as a capsule. In some embodiments, the pharmaceutical composition is encapsulated in a hard gel capsule. In some embodiments, the pharmaceutical composition is encapsulated in a soft gel capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

**[00110]** In some embodiments, the pharmaceutical composition comprising Compound 1 is formulated as a capsule. In some embodiments, the pharmaceutical composition is encapsulated in a hard gel capsule. In some embodiments, the pharmaceutical composition is encapsulated in a soft gel capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

**[00111]** In some embodiments, the capsule is formed using materials which include, but are not limited to, natural or synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, or any combinations thereof. In some embodiments, the capsule is formed using preservatives, coloring and opacifying agents, flavorings and sweeteners, sugars, gastroresistant substances, or any combinations thereof. In some embodiments, the capsule is coated. In some embodiments, the coating covering the capsule includes, but is not limited to, immediate release coatings, protective coatings, enteric or delayed release coatings, sustained release coatings, barrier coatings, seal

coatings, or combinations thereof. In some embodiments, a capsule herein is hard or soft. In some embodiments, the capsule is seamless. In some embodiments, the capsule is broken such that the particulates are sprinkled on soft foods and swallowed without chewing. In some embodiments, the shape and size of the capsule also vary. Examples of capsule shapes include, but are not limited to, round, oval, tubular, oblong, twist off, or a non-standard shape. The size of the capsule may vary comprising the volume of the particulates. In some embodiments, the size of the capsule is adjusted based on the volume of the particulates and powders. Hard or soft gelatin capsules may be manufactured in accordance with conventional methods as a single body unit comprising the standard capsule shape. A single-body soft gelatin capsule typically may be provided, for example, in sizes from 3 to 22 minims (1 minims being equal to 0.0616 ml) and in shapes of oval, oblong or others. The gelatin capsule may also be manufactured in accordance with conventional methods, for example, as a two-piece hard gelatin capsule, sealed or unsealed, typically in standard shape and various standard sizes, conventionally designated as (000), (00), (0), (1), (2), (3), (4), and (5). The largest number corresponds to the smallest size. In some embodiments, the pharmaceutical composition described herein (e.g., capsule) is swallowed as a whole.

**[00112]** In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients.

**[00113]** In some embodiments, the capsule is free of additional excipients.

*Tablet*

**[00114]** In some embodiments, the pharmaceutical composition comprising the crystalline composition comprising Compound I (e.g., comprising Formula I) is formulated as a tablet.

**[00115]** In some embodiments, the pharmaceutical composition comprising Compound 1 is formulated as a tablet.

**[00116]** In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg or less than about 200 mg. In some embodiments, the tablet has a dose strength of more than about 50 mg, more than about 100 mg, more than about 150 mg, more than about 200 mg, or more than about 250 mg. In some embodiments, the tablet size is less than about 1000 mg for a dose strength of more than about 50 mg. In some embodiments, the tablet size is less than 800 mg for a dose strength of more than about 100 mg. In some embodiments, the tablet size is less than 600 mg for a dose strength of more than about 150 mg. In some embodiment, the tablet size is less than 400 mg for a dose strength of more than about 200 mg. In some embodiments, the tablet size is less

than 400 mg for a dose strength of 200 mg. In some embodiments, the tablet size is about 200 mg for a dose strength of about 50 mg.

**[00117]** In some embodiments, more than about 20% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 24 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 12 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 6 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 3 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 2 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than 70% of the tablet is dissolved in 60 minutes in conventional dissolution media.

**[00118]** In some embodiments, the tablet is produced at a commercial scale.

**[00119]** In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

**[00120]** In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete

dry powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of Compound 1. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone, polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

*Oral dosage forms*

**[00121]** In some embodiments, the pharmaceutical composition comprising Compound 1 or the crystalline composition comprising Formula I or is formulated as an oral dosage form. In some embodiments, the oral dosage form is selected from the group consisting of a tablet, a capsule, a buccal tablet, a sub-lingual table, an orally-disintegrating tablet, a thin film, a liquid solution, a liquid suspension, a syrup, a powder, and solid crystals. In some embodiment, the oral dosage form is selected from the group consisting of a tablet, a capsule, a buccal tablet, a sub-lingual table, an orally-disintegrating tablet, a thin film, a liquid solution, a liquid suspension, a syrup, a powder, solid crystals, minitabs, coated pellets and sachets.

**[00122]** Oral dosage forms may include capsules, tablets, pills, powders or granules. Such forms may include forms that dissolve or disintegrate quickly in the oral environment. Such forms may be prepared with coatings and shells. In some embodiments, these oral dosage forms are capable of controlled or sustained release.

*Pharmaceutically Acceptable Excipients*

**[00123]** In some embodiments, the pharmaceutical composition comprising Compound 1 (e.g., crystalline composition comprising Compound 1) or the crystalline composition comprising Formula I comprises a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is free of pharmaceutically acceptable excipients. The term "pharmaceutically acceptable excipient", as used herein, means one or more compatible solid or encapsulating substances, which are suitable for administration to a

mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction, which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. In some embodiments, the pharmaceutically acceptable excipient is of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal, being treated.

**[00124]** Some examples of substances, which can serve as pharmaceutically acceptable excipients include:

- Amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, the amino acid is arginine. In some embodiments, the amino acid is L-arginine.
- Monosaccharides such as glucose (dextrose), arabinose, mannitol, fructose (levulose), and galactose.
- Cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose.
- Solid lubricants such as talc, stearic acid, magnesium stearate and sodium stearyl fumarate.
- Polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol.
- Emulsifiers such as the polysorbates.
- Wetting agents such as sodium lauryl sulfate, Tween®, Span , alkyl sulphates, and alkyl ethoxylate sulphates.
- Cationic surfactants such as cetrimide, benzalkonium chloride, and cetylpyridinium chloride.
- Diluents such as calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose.
- Binders such as starches (corn starch and potato starch), gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC).
- Disintegrants such as starch, and alginic acid.
- Super-disintegrants such as ac-di-sol, croscarmellose sodium, sodium starch glycolate and crospovidone.

- Glidants such as silicon dioxide.
- Coloring agents such as the FD&C dyes.
- Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors.
- Preservatives such as benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate, phenylmercuric nitrate, parabens, and sodium benzoate.
- Tonicity adjustors such as sodium chloride, potassium chloride, mannitol, and glycerin.
- Antioxidants such as sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA.
- pH adjuster such as NaOH, sodium carbonate, sodium acetate, HCl, and citric acid.
- Cryoprotectants such as sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran.
- Surfactants such as sodium lauryl sulfate. For example, cationic surfactants such as cetrimide (including tetradecyl trimethyl ammonium bromide with dodecyl and hexadecyl compounds), benzalkonium chloride, and cetylpyridinium chloride. Some examples of anionic surfactants are alkylsulphates, alkylethoxylate sulphates, soaps, carboxylate ions, sulfate ions, and sulfonate ions. Some examples of non-ionic surfactants are polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glocol, glycerol esters, sorbitan derivatives, polyethylene glycol (such as PEG-40, PEG-50, or PEG-55) and esters of fatty alcohols.
- Organic materials such as carbohydrates, modified carbohydrates, lactose (including a-lactose, monohydrate spray dried lactose or anhydrous lactose), starch, pregelatinized starch, sucrose, mannitol, sorbital, cellulose (including powdered cellulose and microcrystalline cellulose).
- Inorganic materials such as calcium phosphates (including anhydrous dibasic calcium phosphate, dibasic calcium phosphate or tribasic calcium phosphate).
- Co-processed diluents.
- Compression aids.
- Anti-tacking agents such as silicon dioxide and talc.

**[00125]** In some embodiments, the pharmaceutical composition comprises the crystalline composition comprising Formula I.

**[00126]** In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprises Compound 1.

**[00127]** In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 95% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 90% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 85% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 80% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 70% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 65% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 20% by weight of the dosage form.

**[00128]** In some embodiments, the pharmaceutical composition comprises a diluent in about 95% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 90% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 85% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 80% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 70% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 65% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises

a diluent in about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 20% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% by weight of the dosage form.

**[00129]** In some embodiments, the pharmaceutical composition comprises a second diluent. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 95% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 90% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 85% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 80% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 70% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 65% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 40% by weight of the dosage

form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 20% by weight of the dosage form.

**[00130]** In some embodiments, the pharmaceutical composition comprises a second diluent in about 95% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 90% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 85% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 80% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 70% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 65% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 20% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% by weight of the dosage form.

**[00131]** In some embodiments, the diluent is selected from calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose. In some embodiments, the diluent is lactose monohydrate. In some embodiments, the diluent is microcrystalline cellulose. In some embodiments, the diluent is calcium carbonate. In some embodiments, the diluent is calcium phosphate. In some embodiments, the diluent is starch. In some embodiments, the diluent is pregelatinized starch. In some embodiments, the diluent is sodium carbonate. In some embodiments, the diluent is mannitol.

**[00132]** In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 9% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 2% by weight of the dosage form.

**[00133]** In some embodiments, the pharmaceutical composition comprises a binder in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 9% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 2% by weight of the dosage form. In

some embodiments, the pharmaceutical composition comprises a binder in about 1% by weight of the dosage form.

**[00134]** In some embodiments, the binder is selected from starches (corn starch and potato starch), gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC). In some embodiments, the binder is hydroxypropyl cellulose (HPC). In some embodiments, the binder is starch. In some embodiments, the binder is gelatin. In some embodiments, the binder is polyvinylpyrrolidone (PVP). In some embodiments, the binder is hydroxypropyl methyl cellulose (HPMC).

**[00135]** In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 4.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 4.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 3.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 3.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 2.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 2.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 1.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 1% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 0.8% by weight of the dosage form.

**[00136]** In some embodiments, the pharmaceutical composition comprises a surfactant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 4.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 4.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 3.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 3.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 2.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 2.0% by weight of the dosage form. In some embodiments,

the pharmaceutical composition comprises a surfactant in about 1.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 1% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.1% by weight of the dosage form.

**[00137]** In some embodiments, the surfactant is selected from sodium lauryl sulfate, cetrimide, benzalkonium chloride, cetylpyridinium chloride, alkylsulphates, alkylethoxylate sulphates, soaps, carboxylate ions, sulfate ions, sulfonate ions, polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glocol, glycerol esters, sorbitan derivatives, polyethylene glycol (such as PEG-40, PEG-50, or PEG-55) and esters of fatty alcohols. In some embodiments, the surfactant is sodium lauryl sulfate.

**[00138]** In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 9% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 1.5% by weight of the dosage form.

**[00139]** In some embodiments, the pharmaceutical composition comprises a disintegrant in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 9% by weight of the dosage form. In some

embodiments, the pharmaceutical composition comprises a disintegrant in about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% by weight of the dosage form.

**[00140]** In some embodiments, the disintegrant is selected from starch, alginic acid, ac-di-sol, croscarmellose sodium, sodium starch glycolate, and crospovidone. In some embodiments the disintegrant is croscarmellose sodium. In some embodiments the disintegrant is sodium starch glycolate. In some embodiments the disintegrant is crospovidone.

**[00141]** In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 2% by weight of the dosage form.

**[00142]** In some embodiments, the pharmaceutical composition comprises a glidant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% by weight of the dosage form.

**[00143]** In some embodiments the glidant is colloidal silicon dioxide.

**[00144]** In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in

about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% to about 2% by weight of the dosage form.

**[00145]** In some embodiments, the pharmaceutical composition comprises a lubricant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% by weight of the dosage form.

**[00146]** In some embodiments the lubricant is selected from talc, stearic acid, magnesium stearate and sodium stearyl fumarate. In some embodiments, the lubricant is talc. In some embodiments, the lubricant is stearic acid. In some embodiments, the lubricant is magnesium stearate. In some embodiments, the lubricant is sodium stearyl fumarate.

**[00147]** In some embodiments, the pharmaceutical composition comprises a granulating agent. In some embodiments, the granulating agent is purified water.

**[00148]** In some embodiments, the pharmaceutical composition comprises a first diluent in about 10% to about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 10% to about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 0.5% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 0.5% to about 5%.

**[00149]** In some embodiments, the pharmaceutical composition comprises a first diluent in about 35% to about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 15% to about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a

disintegrant in about 2% to about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 0.5% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 0.5% to about 3% by weight of the dosage form.

*Amounts*

**[00150]** In some embodiments, the pharmaceutical composition comprises between about 50 mg and about 200 mg. In some embodiments, the pharmaceutical composition comprises about 50 mg. In some embodiments, the pharmaceutical composition comprises about 200 mg. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 500 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 450 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 400 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 350 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 300 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 250 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 200 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 175 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 150 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 125 mg of the crystalline composition comprising Compound 1 (e.g.,comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 100 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 90 mg of the crystalline comprising

Compound 1 (e.g., composition comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 80 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 70 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 60 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 50 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 40 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 30 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 20 mg of the crystalline composition comprising Compound 1 (e.g.,comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 10 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 9 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 8 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 7 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 6 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 5 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 4 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 3 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments,

the pharmaceutical composition comprises between about 1 mg and about 2 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[00151]** In some embodiments, the pharmaceutical composition comprises between about 500 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 450 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 400 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 350 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 300 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I. In some embodiments, the pharmaceutical composition comprises between about 250 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 200 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 150 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 100 mg of the crystalline comprising Compound 1 (e.g., composition comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 90 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 80 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 70 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 60 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 50 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 40 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 30 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some

embodiments, the pharmaceutical composition comprises between about 20 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 10 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 5 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

**[00152]** In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises between about 50 mg and about 200 mg of Compound 1. In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises about 50 of Compound 1. In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises about 100 of Compound 1. In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises about 200 of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 450 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 400 mg Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 350 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 300 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 250 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 200 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 175 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 150 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 125 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 100 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 90 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 80 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and

about 70 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 60 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 50 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 40 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 30 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 20 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 10 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 9 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 8 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 7 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 6 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 5 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 4 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 3 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 2 mg of Compound 1.

**[00153]** In some embodiments, the pharmaceutical composition comprises about 500 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 450 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 350 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 70 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 50

mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 40 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 5 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 1 mg Compound 1.

**[00154]** In some embodiments, the pharmaceutical composition comprises Compound I in about 25 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in about 10 % to about 50 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in about 10 % to about 15 %, about 10 % to about 20 %, about 10 % to about 25 %, about 10 % to about 30 %, about 10 % to about 35 %, about 10 % to about 40 %, about 10 % to about 45 %, about 10 % to about 50 %, about 15 % to about 20 %, about 15 % to about 25 %, about 15 % to about 30 %, about 15 % to about 35 %, about 15 % to about 40 %, about 15 % to about 45 %, about 15 % to about 50 %, about 20 % to about 25 %, about 20 % to about 30 %, about 20 % to about 35 %, about 20 % to about 40 %, about 20 % to about 45 %, about 20 % to about 50 %, about 25 % to about 30 %, about 25 % to about 35 %, about 25 % to about 40 %, about 25 % to about 45 %, about 25 % to about 50 %, about 30 % to about 35 %, about 30 % to about 40 %, about 30 % to about 45 %, about 30 % to about 50 %, about 35 % to about 40 %, about 35 % to about 45 %, about 35 % to about 50 %, about 40 % to about 45 %, about 40 % to about 50 %, or about 45 % to about 50 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, or about 50 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in at least about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, or about 45 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in at most about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, or about 50 % w/w.

**[00155]** In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 500 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 450 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 400 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to

about 350 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 300 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 250 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 200 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 150 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 100 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 90 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 80 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 70 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 60 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 50 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 40 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 30 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 20 mg.

**[00156]** In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 300 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 200 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 20 mg. In some

embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 10 mg.

**[00157]** In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 300 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 200 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 10 mg.

**[00158]** In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 300 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 200 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 10 mg.

**[00159]** In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 100 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 90 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 80 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 70 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 60 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 5 mg.

**[00160]** In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises

a binder in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 1 mg.

**[00161]** In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 9 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 8 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 7 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 6 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 5 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 4 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 3 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 2 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 1.5 mg.

**[00162]** In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is

about 20 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1.75 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1.5 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1.25 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1 mg.

**[00163]** In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 100 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 90 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 80 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 70 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 60 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 50 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 40 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 30 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 20 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 10 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 9 mg. In some embodiments,

the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 8 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 7 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 6 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 5 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 4 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 3 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 2 mg.

**[00164]** In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 2 mg. In

some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 1 mg.

**[00165]** In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 45 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 35 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 25 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 15 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 5 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 2 mg.

**[00166]** In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 3 mg. In some

embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 1 mg.

**[00167]** In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 45 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 35 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 25 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 15 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 5 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 2 mg.

**[00168]** In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 4 mg. In some

embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 1 mg.

**[00169]** In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is between about 1 mg to about 200 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is between about 1 mg to about 200 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg to about 50 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg to about 50 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg to about 50 mg by weight of the dosage form.

**[00170]** In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and 20 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg to about 10 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 20 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg to about 20 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg to about 20 mg by weight of the dosage form.

***Particle size***

**[00171]** In some embodiments, the pharmaceutical composition (e.g., comprising the crystalline composition comprising Compound 1 (e.g., comprising Formula I)) is in the form

of microparticles. In some embodiments, microparticles of the crystalline composition comprising Compound 1 (e.g., comprising Formula I) have an average size from about 1 μm to about 100 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 90 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 80 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 70 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 60 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 50 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 40 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 30 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 20 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 10 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 5 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 100 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 90 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 80 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 70 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 60 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 50 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 40 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 30 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 20 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 10 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 9 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 8 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 7 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 6 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 5 μm. In some embodiments,

microparticles of the crystalline composition have an average size from about 4 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 3 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 2 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 100 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 90 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 80 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 70 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 60 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 50 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 40 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 30 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 20 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 10 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 5 μm.

**[00172]** In some embodiments, the pharmaceutical composition comprises the crystalline composition comprising Compound 1 (e.g., comprising Formula I), wherein the crystalline composition has a D90 from about 1 μm to about 50 μm. In some embodiments, the crystalline composition has a D90 from about 1 μm to about 20 μm, from about 2 μm to about 19 μm, from about 3 μm to about 18 μm, from about 4 μm to about 17 μm, from about 5 μm to about 16 μm, from about 6 μm to about 15 μm, from about 7 μm to about 14 μm, from about 8 μm to about 13 μm, from about 9 μm to about 13 μm, or from about 8 μm to about 12 μm. In some embodiments, the pharmaceutical composition comprises the crystalline composition comprising Compound 1 (e.g., comprising Formula I), wherein the crystalline composition has a D90 of more than about 1 μm, more than about 2 μm, more than about 3 μm, more than about 4 μ, more than about 5 μm, more than about 6 μm, more than about 7 μm, more than about 8 μm, more than about 9 μm, more than about 10 μm, more than about 11 μm, more than about 12 μm, more than about 13 μm, more than about 14 μm more than about 15 μm more than about 16 μm, more than about 17 μm, more than about 18 μm, or more than about 19 μm. In some embodiments, the crystalline composition has a

D90 of less than about 20 μm, less than about 19 μm, less than about 18 μm, less than about 17 μm, less than about 16 μm, less than about 15 μm, less than about 14 μm, less than about 13 μm, less than about 12 μm, or less than about 11 μm.

**[00173]** In some embodiments, the pharmaceutical composition comprising Compound 1 is in the form of microparticles. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 100 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 90 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 80 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 70 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 60 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 50 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 40 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 30 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 20 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 5 μm. In some embodiments, microparticles of Compound 1 have an average size from about 100 μm. In some embodiments, microparticles of Compound 1 have an average size from about 90 μm. In some embodiments, microparticles of Compound 1 have an average size from about 80 μm. In some embodiments, microparticles of Compound 1 have an average size from about 70 μm. In some embodiments, microparticles of Compound 1 have an average size from about 60 μm. In some embodiments, microparticles of Compound 1 have an average size from about 50 μm. In some embodiments, microparticles of Compound 1 have an average size from about 40 μm. In some embodiments, microparticles of Compound 1 have an average size from about 30 μm. In some embodiments, microparticles of Compound 1 have an average size from about 20 μm. In some embodiments, microparticles of Compound 1 have an average size from about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 9 μm. In some embodiments, microparticles of Compound 1 have an average size from about 8 μm. In some embodiments, microparticles of Compound 1 have an average size from about 7 μm. In some embodiments, microparticles of Compound 1 have an average size from about 6 μm. In some embodiments, microparticles of Compound 1 have an average size from about 5 μm. In some embodiments, microparticles of Compound 1 have an

average size from about 4 μm. In some embodiments, microparticles of Compound 1 have an average size from about 3 μm. In some embodiments, microparticles of Compound 1 have an average size from about 2 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 100 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 90 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 80 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 70 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 60 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 50 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 40 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 30 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 20 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 10 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 5 μm.

**[00174]** In some embodiments, the pharmaceutical composition comprises Compound 1, wherein Compound 1 has a D90 from about 1 μm to about 50 μm. In some embodiments, Compound 1 has a D90 from about 1 μm to about 20 μm, from about 2 μm to about 19 μm, from about 3 μm to about 18 μm, from about 4 μm to about 17 μm, from about 5 μm to about 16 μm, from about 6 μm to about 15 μm, from about 7 μm to about 14 μm, from about 8 μm to about 13 μm, from about 9 μm to about 13 μm, or from about 8 μm to about 12 μm. In some embodiments, the pharmaceutical composition comprises Compound 1 , wherein Compound 1 has a D90 of more than about 1 μm, more than about 2 μm, more than about 3 μm, more than about 4 μ, more than about 5 μm, more than about 6 μm, more than about 7 μm, more than about 8 μm, more than about 9 μm, more than about 10 μm, more than about 11 μm, more than about 12 μm, more than about 13 μm, more than about 14 μm more than about 15 μm more than about 16 μm, more than about 17 μm, more than about 18 μm, or more than about 19 μm. In some embodiments, Compound 1 has a D90 of less than about 20 μm, less than about 19 μm, less than about 18 μm, less than about 17 μm, less than about 16 μm, less than about 15 μm, less than about 14 μm, less than about 13 μm, less than about 12 μm, or less than about 11 μm.

**Methods of Preparing the Crystalline Composition Comprising Compound I (e.g., Comprising Formula I)**

**[00175]** Isolation and purification of the chemical entities and intermediates described herein can be performed, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples below. However, other equivalent separation or isolation procedures can also be used. Prior to crystallization, Compound 1 may be isolated in about 50% chemical purity, 55% chemical purity, 60% chemical purity, 65% chemical purity, 70% chemical purity, 75% chemical purity, 80% chemical purity, 90% chemical purity, 91% chemical purity, 92% purity, 93% chemical purity, 94% chemical purity, 95% chemical purity, 96% chemical purity, 97% chemical purity, 98% chemical purity, 99% chemical purity, about 98% chemical purity, or about 100% chemical purity.

**[00176]** In some embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) disclosed herein are obtained by crystallizing Compound 1 with a chemical purity of less than about 98%, less than about 97%, less than about 96%, less than about 95%, less than about 94%, less than about 93%, less than about 92%, less than about 91%, less than about 90%, less than about 89%, less than about 88%, less than about 87%, less than about 86%, less than about 85%, less than about 84%, less than about 83%, less than about 82%, less than about 81%, less than about 80%, less than about 78%, less than about 76%, less than about 74%, less than about 72%, or less than about 70%. In some embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is obtained by crystallizing Compound 1 with a chemical purity in the range of about 70% to about 99%, 80% to about 96%, about 85% to about 96%, about 90% to about 96%, about 80% to 98%, about 85% to about 98%, about 90% to about 98%, about 92% to about 98%, about 94% to 98%, or about 96% to about 98%.

**Preparation of Crystalline Form I**

**[00177]** In some aspects, the present disclosure provides a method of preparing a crystalline composition comprising Compound I (e.g., comprising Formula I), wherein the method comprises:

(a) dissolving 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) and an acid (e.g., oxalic acid) in a solvent;

(b) heating the solution or slurry from step (a); and

(c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound I (e.g., comprising Formula I).

**[00178]** In some embodiments, the solvent in step (a) comprises acetone, heptane, water, 2-butanol, ethyl acetate, 2-propanol, methyl tert-butyl ether, ethanol, methyl ethyl ketone, 1-pentanol, or a combination thereof. In some embodiments, the solvent in step (a) is heptane. In some embodiments, the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone. In some embodiments, the solvent in step (a) is a mixture of heptane and methyl ethyl ketone.

**[00179]** In some embodiments, step (b) is heated at about 50 °C. In some embodiments, step (b) is heated to at least about 50 °C.

**[00180]** In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between about 20 mg/mL and about 300 mg/mL. In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between about 40 mg/mL and about 250 mg/mL. In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between about 100 mg/mL and about 200 mg/mL. In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between 125 mg/mL and about 175 mg/mL.

**[00181]** In various embodiments, the method of preparing the crystalline composition comprising Compound I (e.g., comprising Formula I) involves recrystallization of Compound 1 from a binary, tertiary, or greater solvent system, collectively understood as a multi-solvent system. In some embodiments, the method of preparing the crystalline composition comprising Compound I (e.g., comprising Formula I) involves crystallization from a mono- or multi-solvent system, where the crystallization involves dissolving Compound 1 in the mono- or multi-solvent system at a temperature above ambient temperature. In some embodiments, the dissolving of Compound 1 in the mono- or multi-solvent system is performed at a temperature of about 0-90 °C, 5-90 °C, 10-90 °C, 15-90 °C, 20-90 °C, 25-90 °C, 30-90 °C, 35-90 °C, 40-90 °C, 45-90 °C, 50-90 °C, 55-90 °C, 60-90 °C, 65-90 °C, 70-90 °C, 75-90 °C, 80-90 °C, 85-90 °C, 0-80 °C, 5-80 °C, 10-80 °C, 20-80 °C, 30-80 °C, 40-80 °C, 50-80 °C, 60-80 °C, 70-80 °C, 0-70 °C, 5-70 °C, 10-70 °C, 15-70 °C, 20-70 °C, 30-70 °C, 40-70 °C, 50-70 °C, 60-70 °C, 0-60 °C, 10-60 °C, 20-60 °C, 30-60 °C, 40-60 °C, or 50-60 °C.

**[00182]** In various embodiments, the crystallization further involves actively heating the solution containing the dissolved Compound 1, for example to a temperature of about 40-100

°C, 40-90 °C, 40-80 °C, 40-70 °C, 40-60 °C, 40-50 °C, 50-100 °C, 50-90 °C, 50-80 °C, 50-70 °C, 50-60 °C, 60-100 °C, 60-90 °C, 60-80 °C, 60-70 °C, 70-100 °C, 70-90 °C, 70-80 °C, 80-100 °C, or 80-90 °C. In various embodiments, the solution containing the dissolved Compound 1 is maintained at the heated temperature for a period of time, for example for about 30 min, about 1 h, about 2 h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h, about 11 h, about 12 h, about 13 h, about 14 h, about 15 h, about 16 h, about 17 h, about 18 h, about 19 h, about 20 h, about 21 h, about 22 h, about 23 h, about 24 h or more.

**[00183]** In various embodiments, the crystallization further involves actively cooling the heated solution containing the dissolved Compound 1, for example to a temperature of about 0-40 °C, 0-30 °C, 0-20 °C, 0-10 °C, 10-40 °C, 10-30 °C, 10-20 °C, 20-40 °C, 20-30 °C, 20-10 °C, or 30 °C-40 °C. In some embodiments, the crystallization further involves actively cooling the heated solution containing the dissolved Compound 1 to a temperature of about 20-30 °C. In various embodiments, the solution containing the dissolved Compound 1 is further maintained at this lower temperature for a time period, for example for about 30 min, about 1 h, about 2 h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h, about 11 h, about 12 h, about 13 h, about 14 h, about 15 h, about 16 h, about 17 h, about 18 h, about 19 h, about 20 h, about 21 h, about 22 h, about 23 h, about 24 h or more.

**[00184]** In various embodiments, the steps of active heating followed by active cooling are repeated multiple times, for example at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 times. In some embodiments, the steps of active heating followed by active cooling are repeated 2, 3, 4, 5, 6, 7, 8, 9, or 10 times.

**[00185]** In various embodiments, the crystallization further involves filtering the solution containing the obtained crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I). In some embodiments, the crystallization optionally involves washing the obtained crystals by a solvent, for example by the recrystallization solvent one or more times. In some embodiments, the crystallization optionally involves drying the obtained crystals, for example under vacuum.

**[00186]** In some embodiments, the chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than 60%, 70%, 80%, 90%, 95%, or 99%. In some embodiments, the chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than about 90%. In some embodiments, the chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than about 95%. In some embodiments, the chemical purity of the

crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than about 99%. The chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) may be measured by any available analytical technique, for example by HPLC analysis.

**[00187]** In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is dry. In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is non-solvated. In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is non-hydrated. In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is anhydrous.

**Methods of Treatment**

**[00188]** In another aspect, the present disclosure provides a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound 1 as described herein, or a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the subject has congenital adrenal hyperplasia (CAH).

**[00189]** In another aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or a pharmaceutical composition comprising a crystalline composition comprising Formula I as described herein. In some embodiments, the CAH is classic CAH. In some embodiments, the CAH is non-classical CAH.

**[00190]** In another aspect, the present disclosure provides a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the hyperandrongic symptoms are selected from the group consisting of acne, hirsutism, and alopecia.

**[00191]** In another aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein.

**[00192]** In another aspect, the present disclosure provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering to the subject a a composition comprising Compound I, or crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the metabolic symptoms are selected from the group consisting of body weight, BMI, fat mass, waist circumference, blood pressure and glycemic control.

**[00193]** In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein.

**[00194]** In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein.

**[00195]** In another aspect, the present disclosure provides a method of treating endometriosis or improving the symptoms of endometriosis in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition improves the symptom of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the

pharmaceutical composition reduces the symptoms of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition prevents the symptom of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition eliminates the symptom of pain experienced by the subject.

**[00196]** In some embodiments, the methods described herein result in the reduction of a hormone level. Such hormones include deoxycorticosterone, 11-deoxycortisol, Cortisol, corticosterone, aldosterone, pregnenolone, hydroxy pregnenolone, progesterone, 17a-hydroxy progesterone (17-OHP), dehydroepiandrosterone, androstenediol, androstenedione, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein result in the reduction of 17a-hydroxy progesterone (17-OHP). In some embodiments, the methods described herein result in the reduction of adrenocorticotropic hormone (ACTH), also known as corticotropin.

**[00197]** In various embodiments of the methods as described herein, a composition comprising Compound I, or the crystalline composition or the pharmaceutical composition (e.g., comprising Compound 1) is administered at a dose from about 5 mg/day to about 1000 mg/day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fed state. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fasted state. In some embodiments, the crystalline composition or the pharmaceutical composition is administered at least once per day.

**[00198]** In some embodiments of the methods described herein, the composition, or the crystalline composition or the pharmaceutical composition is administered at bedtime. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical composition described herein less than about 4 hours before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical composition described herein less than about 3 hours before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical composition described herein less than about 2 hours before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical compositions described herein less than about 1 hour before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical compositions described herein less than about 30 mins before sleep.

**[00199]** In some embodiments, the methods described herein include administration of the crystalline composition (e.g., comprising Compound 1) or the pharmaceutical compositions (e.g., comprising Compound 1) described herein at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical compositions described herein about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH).

**[00200]** In various embodiments of the methods as described herein, the method further comprises administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen agent. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone. In some embodiments, the additional therapeutic agent is another CRF1antagonist.

**[00201]** In various embodiments of the methods as described herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, or the pharmaceutical composition comprising the crystalline composition as described herein. In some embodiments, the additional therapy is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, or the pharmaceutical composition comprising the crystalline composition as described herein.

**[00202]** In various embodiments of the methods, the subject is from about 9 years of age to about 18 years of age. In some embodiments, the subject is from about 8 years of age to about 55 years of age.

**[00203]** In some aspects, described herein are crystalline compositions comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3- fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propynyl)-1,3-thiazol- 2-amine ("crinecerfont"). In some embodiments, crinecerfont is a salt (e.g., hydrochloric acid salt, p-toluenesulfonic acid salt, etc.). Pharmaceutically acceptable acid addition salts of crinecerfont may be formed by combining a compound having a basic moiety with inorganic acids and organic acids. Inorganic acids which may be used to prepare salts of crinecerfont include, for example,

hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids which may be used to prepare salts of crinecerfont include, for example, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and the like. Pharmaceutically acceptable base addition salts of crinecerfont may be formed by combining a compound having an acidic moiety with inorganic and organic bases. Inorganic bases which may be used to prepare salts of crinecerfont include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, manganese, aluminum hydroxides, carbonates, bicarbonates, phosphates, and the like. In some embodiments, the inorganic base salt is ammonium, potassium, sodium, calcium, and magnesium hydroxides, carbonates, bicarbonates, or phosphates. Organic bases from which may be used to prepare salts of crinecerfont include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Generally, such salts of crinecerfont may be prepared by reacting the free acid or base forms of these compounds with at least a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN). In some embodiments, they crystalline composition comprises crinecerfont and oxalic acid.

**[00204]** In some embodiments, the crystalline composition comprising crinecerfont comprises crinecerfont and an acid in a ratio of crinecerfont to acid of about 2:1, about 1:1, or about 1:2.

**[00205]** In some embodiments, the composition comprising crinecerfont is in a capsule (e.g., an immediate-release capsule or a capsule for opening (e.g., comprising crinecerfont granules).

**[00206]** In some aspects, disclosed herein are methods of administering a composition (e.g., crystalline composition) comprising crinecerfont. In some embodiments, the method further comprises administering an additional therapeutic. In some embodiments, the additional therapeutic. In some embodiments, the additional therapeutic comprises hydrocortisone. In some embodiments, the hydrocortisone is an immediate-release hydrocortisone. In some embodiments, the hydrocortisone is in a capsule (e.g., a capsule for opening (e.g., hydrocortisone granules in a capsule)). In some embodiments, the hydrocortisone is an modified-release hydrocortisone. In some embodiments, the hydrocortisone is in a hard-capsule (e.g., a modified-release hard capsule).

## ADDITIONAL EMBODIMENTS

**[00207]** The following embodiments are given for the purpose of illustrating various embodiments of the disclosure and are not meant to limit the present disclosure or any aspect thereof (e.g., element) in any fashion. The following embodiments may include additional elements disclosed herein. Changes therein and other uses which are encompassed within the spirit of the disclosure as defined by the scope of the claims will occur to those skilled in the art.

1. A pharmaceutical formulation, comprising:

(a) about 10 mg to about 300 mg of 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-α) pyrimidine (Compound 1), or a pharmaceutically acceptable salt or solvate thereof;

(b) a first diluent in about 40% to about 45% by weight, wherein the first diluent comprises lactose monohydrate;

(c) a second diluent in about 25% by weight, wherein the second diluent comprises microcrystalline cellulose;

(d) about 1% to about 6% by weight of hydroxypropyl cellulose;

(e) about 0.5% to about 5% by weight of sodium lauryl sulfate; and

(f) about 4% by weight of croscarmellose sodium.

2. The pharmaceutical formulation of embodiment 1, further comprising a glidant, wherein the glidant comprises colloidal silicon dioxide.

3. The pharmaceutical formulation of embodiment 1, further comprising a lubricant, wherein the lubricant comprises magnesium stearate.

4. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is about 1% by weight of the pharmaceutical formulation.

5. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is in an amount that is about 2 mg.

6. The pharmaceutical formulation of embodiment 1, wherein Compound 1 or a pharmaceutically acceptable salt thereof is in an amount that is about 50 mg.

7. The pharmaceutical formulation of embodiment 1, wherein the lactose monohydrate is about 40.25% by weight of the pharmaceutical formulation.

8. The pharmaceutical formulation of embodiment 1, wherein the lactose monohydrate is in an amount that is about 80.50 mg.

9. The pharmaceutical formulation of embodiment 1, wherein the microcrystalline cellulose is in an amount that is about 50 mg.

10. The pharmaceutical formulation of embodiment 1, wherein the hydroxypropyl cellulose is about 3% by weight of the pharmaceutical formulation.

11. The pharmaceutical formulation of embodiment 1, wherein the hydroxypropyl cellulose is in an amount that is about 6 mg.

12. The pharmaceutical formulation of embodiment 1, wherein the sodium lauryl sulfate is about 0.75% by weight of the pharmaceutical formulation.

13. The pharmaceutical formulation of embodiment 1, wherein the sodium lauryl sulfate is in an amount that is about 1.50 mg.

14. The pharmaceutical formulation of embodiment 1, wherein the croscarmellose sodium is in an amount that is about 8 mg.

15. The pharmaceutical formulation of embodiment 2, wherein the colloidal silicon dioxide is about 1% by weight of the pharmaceutical formulation.

16. The pharmaceutical formulation of embodiment 2, wherein the colloidal silicon dioxide is in an amount that is about 2 mg.

17. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is about 1% by weight of the pharmaceutical formulation.

18. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is in an amount that is about 2 mg.

19. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is in a tablet form.

20. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is in a granule form.

21. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is in a capsule.

22. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is packaged in a sachet.

## EXAMPLES

**[00208]** The following examples serve to further describe the manner of using the present disclosure. These examples are presented for illustrative purpose and should not serve to limit the true scope of the present disclosure.

**[00209]** In carrying out the procedures of the methods described herein, it is of course to be understood that references to particular buffers, media, reagents, cells, culture conditions, and the like are not intended to be limiting, but are to be read so as to include all related materials

that one of ordinary skill in the art would recognize as being of interest or value in the particular context in which that discussion is presented. For example, it is often possible to substitute on buffer system or culture medium for another and still achieve similar, if not identical, results. Those of skill in the art will have sufficient knowledge of such systems and methodologies so as to able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

**Example 1 – Preparation and Characterization of the Crystalline Composition Comprising Compound I (e.g., comprising Formula I)**

*Preparation of the Crystalline Composition Comprising Compound I (e.g., comprising Formula I)*

**[00210]** A mixture of 185.0 mg (0.441 mmol) of 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (**Compound 1**), 45.0 mg (0.500 mmol) of oxalic acid, and 2.5 mL of diisopropyl ether was agitated. After one hour, an additional 1 mL of diisopropyl ether was added. After stirring overnight, the mixture was vacuum filtered and the resulting solid was dried to afford 170 mg (76%) of the crystalline composition comprising Compound I (e.g., comprising Formula I) as solid.

*X-Ray Powder Diffraction*

**[00211]** X-ray powder diffraction (XPRD) patterns were obtained on a Rigaku Smart-Lab X-ray diffraction system. A CuK source (=0.71073 Å) operating minimally at 40 kV and 44 mA scans each sample between 2 and 40 degrees 2θ. The step size is 0.02° 2θ.

**[00212]** The XRPD pattern obtained for the crystalline composition comprising Compound I (e.g., comprising Formula I) is summarized in Table 1 below and shown in **FIG. 1**.

**Table 1 – XRPD Data of the Crystalline Composition** Comprising Compound I (e.g., **comprising Formula I)**

| Peak # | Angle (° 2-θ) | Intensity (%) | Peak # | Angle (° 2-θ) | Intensity (%) |
|---|---|---|---|---|---|
| **1** | 5.44 | 31 | **26** | 26.58 | 4 |
| **2** | 8.82 | 12 | **27** | 26.80 | 14 |
| **3** | 10.84 | 100 | **28** | 26.94 | 8 |
| **4** | 11.70 | 12 | **29** | 27.62 | 3 |
| **5** | 14.60 | 8 | **30** | 28.00 | 13 |

| **Table 1 – XRPD Data of the Crystalline Composition** Comprising Compound I (e.g., **comprising Formula I)** | | | | | |
|---|---|---|---|---|---|
| **6** | 15.56 | 6 | **31** | 28.86 | 14 |
| 7 | 15.96 | 52 | **32** | 29.54 | 3 |
| **8** | 16.28 | 5 | **33** | 31.26 | 3 |
| **9** | 16.70 | 10 | **34** | 31.66 | 5 |
| **10** | 17.66 | 4 | **35** | 31.88 | 4 |
| **11** | 18.44 | 5 | **36** | 32.16 | 3 |
| **12** | 18.82 | 6 | **37** | 32.48 | 2 |
| **13** | 19.18 | 8 | **38** | 32.86 | 5 |
| **14** | 19.60 | 2 | **39** | 33.46 | 2 |
| **15** | 20.02 | 11 | **40** | 34.36 | 2 |
| **16** | 20.50 | 11 | **41** | 35.02 | 3 |
| **17** | 20.78 | 20 | **42** | 35.44 | 1 |
| **18** | 21.72 | 7 | **43** | 35.98 | 2 |
| **19** | 22.12 | 2 | **44** | 36.72 | 4 |
| **20** | 22.74 | 18 | **45** | 37.04 | 3 |
| **21** | 23.04 | 16 | **46** | 37.80 | 5 |
| **22** | 23.44 | 31 | **47** | 38.28 | 2 |
| **23** | 24.80 | 48 | **48** | 38.90 | 2 |
| **24** | 25.52 | 6 | **49** | 39.20 | 2 |
| **25** | 25.92 | 9 | | | |

*Differential Scanning Calorimetry (DSC)*

**[00213]** Differential scanning calorimetry analysis was carried out on a TA Instruments Q2500 Discovery Series instrument. The instrument temperature calibration was performed using indium. The DSC cell was kept under a nitrogen purge of about 50 mL per minute during each analysis. The sample was placed in a standard, crimpled, aluminum pan and was heated from approximately 25 ºC to 350 ºC at a rate of 10 ºC per minute. The DSC trace of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 2**.

*Thermogravimetric Analysis (TGA)*

**[00214]** Thermogravimetry analyses were carried out using a TA Instruments Discovery TGA 5500 instrument that was cooled using a TA Instruments Refrigerated Cooling System (RCS) 90 chiller. The instrument balance was calibrated using class M weights and temperature calibration was performed by measurement of the Curie point of Alumel®. Sample was loaded onto a platinum sample pan and the pan was loaded into the TG instrument. The pan was heated from ambient temperature to 350 °C at a rate of 10 °C per minute. The instrument was controlled using TA Trios software. The TGA trace of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 3**.

*Dynamic Vapor Sorption (DVS)*

**[00215]** The DVS analysis was carried out on a TA Instruments Q5000 sorption analyzer. The instrument was calibrated with standard weights and a sodium bromide standard for humidity. For each analysis, a portion of the sample was weighed into a metal-coated, quartz pan. Each sample was analyzed at 25 °C with a maximum equilibration time of 60 minutes in 10% relative humidity (RH) steps from 5 to 95% RH (adsorption cycle) and from 95 to 5% RH (desorption cycle). Data collection was performed using Advantage for Q Series version 5.5.23. The percent weight change values were calculated using Microsoft Excel®. The DVS trace of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 4**.

*Infrared (IR)*

**[00216]** The IR spectrum was obtained using a Nicolet iS50 Model 60825 Fourier-transform (FT) IR spectrophotometer equipped with a deuterated triglycine sulfate (DTGS) detector, a potassium bromide (KBr) beamsplitter, and an electronically temperature controlled (ETC) Ever-Glo® IR source. The instrument was configured with a SMART iTR diamond attenuated total reflectance (ATR) sampling accessory. The single beam scan of the background (air) and sample were collected with 128 signal-averaged scans at a resolution of 2 cm-1 over the spectral range 400-4000 cm-1. The wavelength calibration was verified using a certified polystyrene standard. Data collection and processing was performed using Omnic 9.2 software. The IR spectrum of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 5**.

*Proton Nuclear Magnetic Resonance ($^1H$ NMR)*

**[00217]** The 1H NMR spectrum was acquired on a Bruker Avance 400 MHz spectrometer using TopSpin v3.2 software. The sample was dissolved in $CD_3OD$ and the resulting solution was transferred into a 5-mm NMR tube for subsequent data acquisition. Data collection parameters are shown in Table 14. The spectrum was processed using the program MNova and referenced to the chemical shift of the residual protons in $CD_3OD$ (3.31 ppm). The $^1H$ NMR spectrum of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 6**.

*Raman*

**[00218]** The Raman spectrum was acquired utilizing a Thermo Scientific model iS50 Fourier-transform (FT) IR spectrophotometer equipped with a Raman accessory. The system is equipped with an indium gallium arsenide (InGaAs) detector, a calcium fluoride (CaF2) beamsplitter, and a 2.5 W laser operating at 1064 nm. The module was configured with a 180° reflective sampling accessory. A sample was prepared by loading particles onto a glass slide. Each FT-Raman spectrum was collected using 0.50 W laser power with 256 signal-averaged scans at a resolution of 4 cm-1 over the spectral range 100-3700 cm-1. The wavelength calibration was verified using a polystyrene. Data acquisition and processing were performed using Omnic 9.7 software. The Raman spectrum of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 7**.

**Example 2 – Formulation Comprising Compound 1**

***General Manufacturing Procedure***

**[00219]** The relevant excipients were manually sieved and then dry mixed. A binder solution was added and the mixture subjected to wet granulation. The granules were then wet milled and dried. The resulting granules were dry milled and added to other relevant common granules and excipients. The mixture was then compressed into tablets to a target tablet weight.

**[00220]** A granulation was developed with a minimum amount and number of excipients. The granulation comprised of Compound 1 ("Tildacerfont") with a surfactant and a binder and, in some cases, a super-disintegrant. After granulation was successful, other excipients were added to enable compression. These excipients included a compression aid, a lubricant, an anti-tacking agent, and a super-disintegrant.

**[00221] Table 1** below summarizes formulations comprising Tildacerfont in both tablet and granules form.

**Table 2 – Formulation Comprising Tildacerfont**

| Material Description | Function | %w/w | mg/Tablet | Granules |
|---|---|---|---|---|
| | | | 50 mg strength | 50 mg strength |
| Intragranular | | | | |
| Tildacerfont (SPN001) | Active ingredient | 25.00 | 50.00 | 50.00 |
| Lactose Monohydrate, USP/NF, Ph. Eur., JP. (Pharmatose 200M EU) | Diluent | 40.25 | 80.50 | 80.50 |
| Hydroxypropylcellulose USP/NF, Ph. Eur., JP (Klucel EXF) | Binder | 3.00 | 6.00 | 6.00 |
| Sodium Lauryl Sulfate, NF/ Ph. Eur./JP (Kolliphor SLS fine) | Surfactant | 0.75 | 1.50 | 1.50 |
| Microcrystalline Cellulose, NF, Ph.Eur., JP (Avicel PH101) | Diluent | 20.00 | 40.00 | 40.00 |
| Purified Water, USP, Ph. Eur | Granulating agent | QS* | - | - |
| Extragranular | | | | |
| Microcrystalline Cellulose, NF, Ph.Eur., JP (Avicel PH101) | Diluent | 5.00 | 10.00 | 10.00 |
| Croscarmellose Sodium NF, Ph. Eur., JP (Ac-Di-Sol) SD-711 | Disintegrant | 4.00 | 8.00 | 8.00 |
| Colloidal Silicon dioxide USP/NF, Ph. Eur., JP (Aerosil 200) | Glidant | 1.00 | 2.00 | 2.00 |
| Magnesium stearate, NF, Ph. Eur., JP (Hyqual 2257) | Lubricant | 1.00 | 2.00 | 2.00 |
| Total | | 100.00 | 200.00 | 200.00 |

| Table 2 – Formulation Comprising Tildacerfont | | | | |
|---|---|---|---|---|
| Film Coating | | | | |
| Opadry II Yellow 85F42129 | Film former | 3.00 | 6.00 | - |
| Purified Water, USP, Ph. Eur | Coating dispersion medium | QS* | - | - |
| Total | | 100.00 | 206.00 | 200.00 |

**Example 3 – Stability of Crystalline Compositions Comprising Compound 1**

**[00222]** To determine the stability of the crystalline compositions prepared comprising the methods described herein, crystalline compositions comprising Compound 1 and oxalic acid were formulated. Samples of the crystalline composition comprising Compound 1-oxalic acid co-crystal were packed in a transparent low-density polyethylene (LDPE) bag, and closed by twisting the bag and tying it with a strip seal. The transparent LDPE bag was then placed in a black LDPE bag that was twisted and tied with a strip seal. The bags were then placed in a high-density polyethylene container.

**[00223]** The samples were then subjected to accelerated aging conditions (40 ± 2 °C /75 ± 5 % relative humidity (RH)) or long-term storage conditions (25 ± 2 °C / 60 ± 5 % RH). Sample stability measurements in each condition were measured at baseline (before exposure to accelerated aging conditions or long-term storage conditions), and one month, two months, and three months after exposure to said conditions. Sample stability measurements included a description of the sample's physical appearance (e.g., color and form), identification by Fourier-transform infrared spectroscopy (FT-IR), identification by X-ray powder diffraction (XRPD), water content (measured by Karl Fischer (KF) on a % weight/weight basis), identification of related substances (e.g., impurities), and high-performance liquid chromatography ((HPLC) measured on a % weight/weight on an anhydrous basis and solvent free basis).

**[00224]** **Table 3** summarizes the results of the measurements obtained from samples exposed to the accelerated aging conditions over the course of one to three months. **Table 4** summarizes the results of the study obtained from the samples exposed to the long-term storage conditions over the course of one to three months.

**Table 3.** Stability data under accelerated aging conditions.

| Parameter | Specification | Baseline | 1 Month | 2 Months | 3 Months |
|---|---|---|---|---|---|
| **Description** | Off-white to yellow color solid | Light yellow color solid | Light yellow color solid | Light yellow color solid | Light yellow color solid |
| **Identification by FT-IR** | IR spectrum of sample should be concordant with that of reference standard | IR spectrum of sample is concordant with that of reference standard | IR spectrum of sample is concordant with that of reference standard | IR spectrum of sample is concordant with that of reference standard | IR spectrum of sample is concordant with that of reference standard |
| **Identification by XRPD** | Diffractogram of the sample should be consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4 ±0.2° | Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4 | Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.7, 15.9, 23.4 | Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4 | Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4 |
| **Water Content by KF (% w/w)** | NMT 0.5 | 0.02 | 0.09 | 0.02 | 0.08 |
| **Related Substances by HPLC (% area) (see a.-d.)** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **a. C07102401-F-Imp1** | NMT 0.15 | BDRL | BDRL | BDRL | BDRL |
| **b. C07102401-F-Imp2** | NMT 0.15 | BDRL | BDRL | BDRL | BDRL |
| **c. Any unspecified impurity** | NMT 0.10 | BDRL | BDRL | BDRL | BDRL |
| **d. Total impurities** | NMT 1.0 | BDRL | BDRL | BDRL | BDRL |
| **Assay of Compound 1 by HPLC (% w/w on anhydrous basis and solvent free basis)** | NLT 98.0 and NMT 102.0 | 99.9 | 99.2 | 100.1 | 99.2 |

n/a: not applicable; NLT: not less than; NMT; not more than; BDRL: below disregard limit

**[00225]** The above data from **Table 3** indicates that the Compound 1-oxalic acid co-crystal is stable up to 3 months at accelerated aging conditions (40 ± 2 °C /75 ± 5 % RH).

**Table 4.** Stability data under long-term storage conditions.

| Parameter | Specification | Baseline | 1 Month | 2 Months | 3 Months |
|---|---|---|---|---|---|
| **Description** | Off-white to yellow color solid | Light yellow color solid | Light yellow color solid | Light yellow color solid | Light yellow color solid |
| **Identification by FT-IR** | IR spectrum of sample should be | IR spectrum of sample is concordant | IR spectrum of sample is concordant | IR spectrum of sample is concordant | IR spectrum of sample is concordant |

| | | | | | |
|---|---|---|---|---|---|
| | concordant with that of reference standard | with that of reference standard | with that of reference standard | with that of reference standard | with that of reference standard |
| **Identification by XRPD** | Diffractogram of the sample should be consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4 ±0.2° | Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4 | Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 838, 10.8, 11.7, 15.9, 23.4 | Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.7, 10.8, 11.6, 15.9, 23.3 | Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 837, 10.8, 11.6, 15.9, 23.4 |
| **Water Content by KF (% w/w)** | NMT 0.5 | 0.02 | 0.10 | 0.03 | 0.05 |
| **Related Substances by HPLC (% area) (see a.-d.)** | | | | | |
| **a. C07102401-F-Imp1** | NMT 0.15 | BDRL | BDRL | BDRL | BDRL |
| **b. C07102401-F-Imp2** | NMT 0.15 | BDRL | BDRL | BDRL | BDRL |

| | | | | | |
|---|---|---|---|---|---|
| **c. Any unspecified impurity** | NMT 0.10 | BDRL | BDRL | BDRL | BDRL |
| **d. Total impurities** | NMT 1.0 | BDRL | BDRL | BDRL | BDRL |
| **Assay of Compound 1 by HPLC (% w/w on anhydrous basis and solvent free basis)** | NLT 98.0 and NMT 102.0 | 99.9 | 99.2 | 100.1 | 99.2 |

n/a: not applicable; NLT: not less than; NMT; not more than; BDRL: below disregard limit

**[00226]** The above data from **Table 4** indicates that the Compound 1-oxalic acid co-crystal is stable up to 3 months at long-term storage conditions (25 ± 2 °C / 60 ± 5 % RH).

**Example 4 – Stability of Crystalline Compositions Comprising Compound 1 for 6 Months**

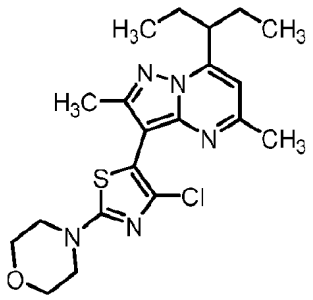
**[00227]** Samples of the crystalline composition comprising Compound 1-oxalic acid co-crystal prepared in Example 3 are subjected to accelerated aging conditions (40 ± 2 °C /75 ± 5 % relative humidity (RH)) or long-term storage conditions (25 ± 2 °C / 60 ± 5 % RH). Sample stability measurements in each condition are measured at baseline (before exposure to accelerated aging conditions or long-term storage conditions), and four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, fourteen months, sixteen months, and eighteen months after exposure to said conditions. Sample stability measurements include a description of the sample's physical appearance (e.g., color and form), identification by Fourier-transform infrared spectroscopy (FT-IR), identification by X-ray powder diffraction (XRPD), water content (measured by Karl Fischer (KF) on a % weight/weight basis), identification of related substances (e.g., impurities), and high-performance liquid chromatography ((HPLC) measured on a % weight/weight on an anhydrous basis and solvent free basis).

**[00228]** The samples of the crystalline composition comprising Compound 1-oxalic acid co-crystal will be stable at four months, five months, six months, seven months, eight months,

nine months, ten months, eleven months, twelve months, fourteen months, sixteen months, and eighteen months after exposure to said conditions, as demonstrated by sample stability measurements. Said sample stability measurements at four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, fourteen months, sixteen months, and eighteen months after exposure to said conditions will be in accordance with the results listed in **Table 3** and **Table 4**.

## CLAIMS

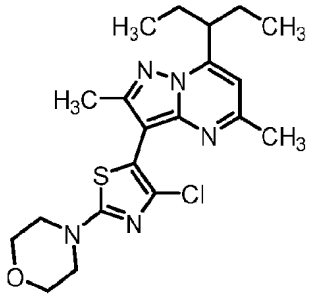
1. A pharmaceutical composition comprising a CRF1 antagonist, wherein the composition is characterized by an X-ray powder diffraction pattern comprising a peak selected from any one or more of 10.84 = 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ.
2. The pharmaceutical composition of claim 1, wherein the composition is measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å .
3. The pharmaceutical composition of claim 1 or 2, wherein the X-ray powder diffraction pattern further comprising at least one peak selected from 5.44 ± 0.2° 2-θ, 20.78 ± 0.2° 2-θ, 22.74 ± 0.2° 2-θ, 23.04 ± 0.2° 2-θ, 26.80 ± 0.2° 2-θ, and 28.86 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.
4. The pharmaceutical composition of any one of claims 1 to 3, wherein the X-ray powder diffraction pattern further comprising at least five peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.
5. The pharmaceutical composition of any one of claims 1 to 4, wherein the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C.
6. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram substantially similar to the one set forth in **FIG. 2**.
7. The pharmaceutical composition of any one of claims 1 to 6, wherein the CRF1 antagonist comprises Compound 1:




Compound 1

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

8. The pharmaceutical composition of any one of claims 1 to 7, wherein the pharmaceutical composition is a crystalline pharmaceutical composition.
9. The pharmaceutical composition of claim 8, wherein the crystalline pharmaceutical composition further comprises oxalic acid.
10. The pharmaceutical composition of claim 9, wherein the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1.
11. A pharmaceutical composition comprising a CRF1 antagonist, wherein the pharmaceutical composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C.
12. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C.
13. The pharmaceutical composition of claim 11 or 12, wherein the pharmaceutical composition is characterized by a melting point of about 166 °C.
14. The pharmaceutical composition of any one of claims 11 to 13, wherein the CRF1 antagonist comprises Compound 1:

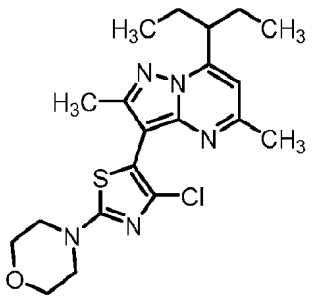



Compound 1

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

15. The pharmaceutical composition of any one of claims 11 to 14, wherein the pharmaceutical composition is a crystalline pharmaceutical composition.
16. The pharmaceutical composition of claim 15, wherein the crystalline pharmaceutical composition further comprises oxalic acid.
17. The pharmaceutical composition of claim 16, wherein the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1.

18. The pharmaceutical composition of any one of claims 11 to 17, wherein the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C.
19. A method of preparing a crystalline composition comprising Compound 1:



Compound 1,

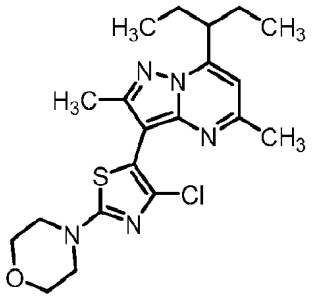
wherein the method comprises:

(a) dissolving Compound 1 and an acid in a solvent;

(b) heating the solution or slurry from step (a); and

(c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound 1.

20. The method of claim 19, wherein the acid comprises oxalic acid.
21. The method of claim 19 or 20, wherein the solvent in step (a) is heptane.
22. The method of claim 19 or 20, wherein the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone.
23. The method of claim 19 or 20, wherein the solvent in step (a) is a mixture of heptane and methyl ethyl ketone.
24. The method of any one of claims 19 to 23, wherein step (b) is heated at about 50 °C.
25. A pharmaceutical composition comprising Compound 1:



Compound 1, or a pharmaceutically acceptable salt or solvate thereof,

wherein Compound 1 is present in an amount of 25% w/w; and

a diluent in about 5% to about 70%

26. The pharmaceutical composition of claim 25, wherein Compound 1 is in an amount of about 50 mg to about 200 mg.
27. The pharmaceutical composition of claim 25, wherein Compound 1 is in an amount of about 50 mg.
28. The pharmaceutical composition of claim 25, wherein the diluent is selected from the group consisting of calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose monohydrate, and a combination thereof.
29. The pharmaceutical composition of claim 28, wherein the diluent is lactose monohydrate.
30. The pharmaceutical composition of claim 29, wherein the lactose monohydrate is about 20% to about 45% by weight of the pharmaceutical composition.
31. The pharmaceutical composition of claim 29, wherein the lactose monohydrate is about 20% to about 40.25% by weight of the pharmaceutical composition.
32. The pharmaceutical composition of claim 31, wherein the lactose monohydrate is in an amount that is about 16.1, 40.25, 80.5, or 322 mg.
33. The pharmaceutical composition of claim 28, wherein the diluent is microcrystalline cellulose.
34. The pharmaceutical composition of claim 28, further comprising a second diluent, wherein the second diluent comprises microcrystalline cellulose
35. The pharmaceutical composition of claim 33, wherein the microcrystalline cellulose is about 25% by weight of the pharmaceutical composition.
36. The pharmaceutical composition of claim 35, wherein the microcrystalline cellulose is in an amount that is about 50 mg.
37. The pharmaceutical composition of claim 25, further comprising a binder, wherein the binder is selected from the group consisting of corn starch and potato starch, gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC), and a combination thereof.
38. The pharmaceutical composition of claim 37, wherein the binder comprises HPC.
39. The pharmaceutical composition of claim 38, wherein the HPC is about 3% by weight of the solid dosage form.

40. The pharmaceutical composition of claim 25, further comprising a surfactant, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate, tetradecyl trimethyl ammonium bromide with dodecyl, hexadecyl compound, benzalkonium chloride, cetylpyridinium chloride, alkylsulphate, alkylethoxylate sulphate, soap, carxylate ion, sulfate ion, sulfonate ion, polyoxyethylene derivative, polyoxypropylene derivative, polyol derivative, polyol ester, polyoxyethylene ester, poloxamers, glocol, glycerol ester, sorbitan derivative, and polyethylene glycol, and a combination thereof.

41. The pharmaceutical composition of claim 40, wherein the surfactant comprises sodium lauryl sulfate.

42. The pharmaceutical composition of claim 41, wherein the sodium lauryl sulfate is about 0.75% by weight of the solid dosage form.

43. The pharmaceutical composition of claim 42, wherein the sodium lauryl sulfate is in an amount that is about 1.5 mg.

44. The pharmaceutical formulation of claim 25, further comprising a disintegrant, wherein the disintegrant is selected from the group consisting of starch, alginic acid, ac-di-sol, croscarmellose sodium, sodium starch glycolate, and crospovidone, and a combination thereof.

45. The pharmaceutical formulation of claim 44, wherein the disintegrant comprises croscarmellose sodium.

46. The pharmaceutical formulation of claim 25, further comprising a glidant, wherein the glidant comprises colloidal silicon dioxide.

47. The pharmaceutical formulation of claim 46, wherein the colloidal silicon dioxide is about 1% by weight of the solid dosage form.

48. The pharmaceutical formulation of claim 46, wherein the colloidal silicon dioxide is in an amount that is about 2 mg.

49. The pharmaceutical formulation of claim 25, further comprising a lubricant, wherein the lubricant is selected from the group consisting of talc, stearic acid, magnesium stearate, sodium stearyl fumarate, and a combination thereof.

50. The pharmaceutical formulation of claim 25, wherein the pharmaceutical formulation is in a solid dosage form.

51. The pharmaceutical formulation of claim 50, wherein the solid dosage form is a tablet.

52. The pharmaceutical formulation of claim 50, wherein the solid dosage form is a granules form.

53. The pharmaceutical formulation of claim 52, wherein said granules form is packaged in a capsule.

54. The pharmaceutical formulation of claim 52, wherein said granules form is packaged in a sachet.

55. A pharmaceutical formulation, comprising:

(a) about 10 mg to about 300 mg of 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-α) pyrimidine (Compound 1), or a pharmaceutically acceptable salt or solvate thereof;

(b) a first diluent in about 40% to about 45% by weight, wherein the first diluent comprises lactose monohydrate;

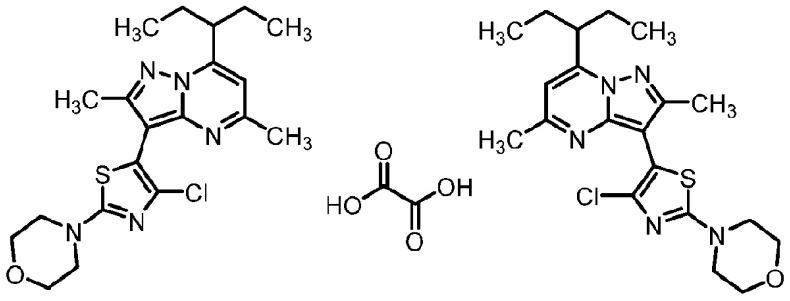
(c) a second diluent in about 25% by weight, wherein the second diluent comprises microcrystalline cellulose;

(d) about 1% to about 6% by weight of hydroxypropyl cellulose;

(e) about 0.5% to about 5% by weight of sodium lauryl sulfate; and

(f) about 4% by weight of croscarmellose sodium.

56. A crystalline composition comprising Formula I:



Formula I.

57. The crystalline composition of claim 56, wherein the crystals have unit cell parameters at T = 150°K of: a = 34.003(4) Å, b = 6.5843(13) Å, c = 21.062(5) Å; β = 108.703(12)°, V = 4466.5(15) $Å^3$ and a monoclinic C2/c space group.

58. The crystalline composition of claim 56, wherein the crystalline composition is characterized by:

(a) an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å;

(b) an X-ray powder diffraction pattern substantially the same as shown in FIG. 1;

(c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C;

(d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C;

(e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2;

(f) a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C;

(g) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3; or

(h) combinations thereof.

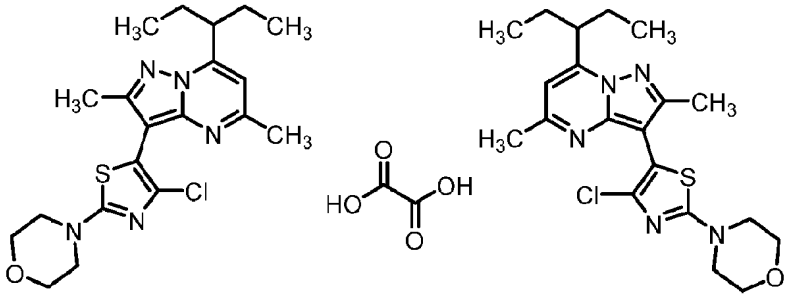
59. The crystalline composition of any one of claim 56, wherein the crystalline composition is characterized by an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

60. The crystalline composition of claim 59, wherein the X-ray powder diffraction pattern further comprising at least one peak selected from 5.44 ± 0.2° 2-θ, 20.78 ± 0.2° 2-θ, 22.74 ± 0.2° 2-θ, 23.04 ± 0.2° 2-θ, 26.80 ± 0.2° 2-θ, and 28.86 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

61. The crystalline composition of claim 59, wherein the X-ray powder diffraction pattern further comprising at least five peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

62. The crystalline composition of any one of claims 56 to 61, wherein the crystalline composition is characterized by an X-ray powder diffraction pattern substantially the same as shown in FIG. 1.

63. The crystalline composition of any one of claims 56 to 62, wherein the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C.
64. The crystalline composition of any one of claims 56 to 62, wherein the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C.
65. The crystalline composition of any one of claims 56 to 64, wherein the crystalline composition is characterized by a melting point of about 166 °C.
66. The crystalline composition of any one of claims 56 to 65, wherein the crystalline composition if characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2.
67. The crystalline composition of any one of claims 56 to 66, wherein the crystalline composition is characterized by a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3.
68. The crystalline composition of any one of claims 56 to 67, wherein the crystalline composition is characterized by a dynamic vapor sorption (DVS) trace substantially the same as shown in FIG. 4.
69. A method of preparing a crystalline composition comprising Formula I:



Formula I,

wherein the method comprises:

(a) dissolving 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) and oxalic acid in a solvent;

(b) heating the solution or slurry from step (a); and

(c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Formula I.

70. The method of claim 69, wherein the solvent in step (a) comprises acetone, heptane, water, 2-butanol, ethyl acetate, 2-propanol, methyl tert-butyl ether, ethanol, methyl ethyl ketone, 1-pentanol, or a combination thereof.
71. The method of claim 70, wherein the solvent in step (a) is heptane.
72. The method of claim 70, wherein the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone.
73. The method of claim 70, wherein the solvent in step (a) is a mixture of heptane and methyl ethyl ketone.
74. The method of claim 69, wherein step (b) is heated at about 50 °C.
75. A method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, comprising administering the subject the crystalline composition of any one of the preceding claims.
76. The method of claim 75, wherein the subject has congenital adrenal hyperplasia (CAH).
77. A method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
78. The method of claim 77, wherein the CAH is classic CAH.
79. The method of claim 77, wherein the CAH is non-classical CAH.
80. A method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
81. The method of claim 80, wherein the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism, and alopecia.
82. A method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
83. A method of improving metabolic symptoms in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
84. The method of claim 83, wherein the metabolic symptoms are selected from the group consisting of body weight, BMI, fat mass, waist circumference, blood pressure and glycemic control.
85. A method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a

subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.

86. A method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, administering to the subject the crystalline composition of any one of the preceding claims.
87. A method of treating endometriosis or improving the symptoms of endometriosis in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
88. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition improves the symptom of pain experienced by the subject.
89. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition reduces the symptom of pain experienced by the subject.
90. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition prevents the symptom of pain experienced by the subject.
91. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition eliminates the symptom of pain experienced by the subject.
92. The method of any one of claims 75 to 87, wherein the crystalline composition or the pharmaceutical composition is administered at a dose from about 5 mg/day to about 1000 mg/day.
93. The method of any one of claims 75 to 92, wherein the crystalline composition or the pharmaceutical composition is 75to in a fed state.
94. The method of any one of claims 75 to 92, wherein the crystalline composition or the pharmaceutical composition is administered in a fasted state.
95. The method of any one of claims 75 to 94, wherein the crystalline composition or the pharmaceutical composition is administered at least once per day.
96. The method of any one of claims 75 to 95, furthering comprising administering to the subject an additional therapeutic agent.
97. The method of anyone of the preceding claims, wherein the method further comprises administering an additional therapeutic agent, wherein the additional therapeutic agent is glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen agent.
98. The method of claim 97, wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.
99. The method of claim 97, wherein the mineralocorticoid is fludrocortisone.

100. The method of claim 97, wherein the additional therapeutic agent is another $CRF_1$ antagonist.

101. The method of any one of claims 75 to 100, further comprising an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

102. The method of claim 101, wherein the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the crystalline composition of any one of the preceding claims.

103. The method of any one of claims 75 to 97, wherein the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the crystalline composition of any one of the preceding claims.

104. The method of any one of the preceding claims, wherein the subject is from about 9 years of age to about 18 years of age.

105. The method of any one of the preceding claims, wherein the subject is from about 8 years of age to about 55 years of age.

FIG. 1

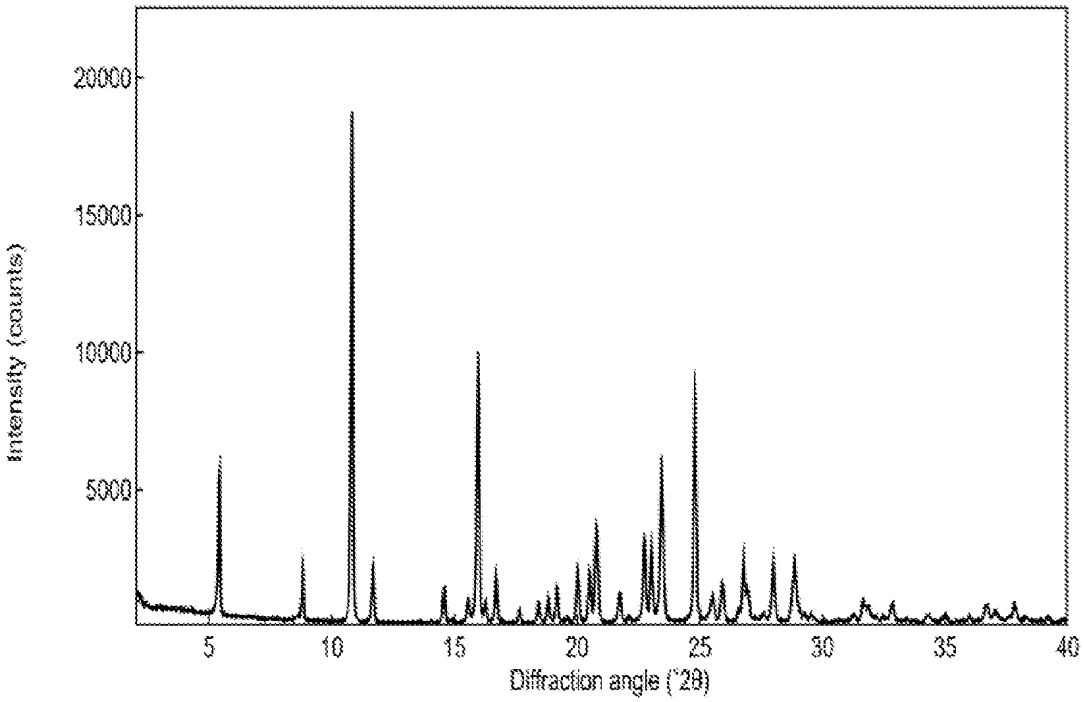

20000
15000
10000
5000
Intensity (counts)
5
10
15
20
25
30
35
40
Diffraction angle (°2θ)

FIG. 2

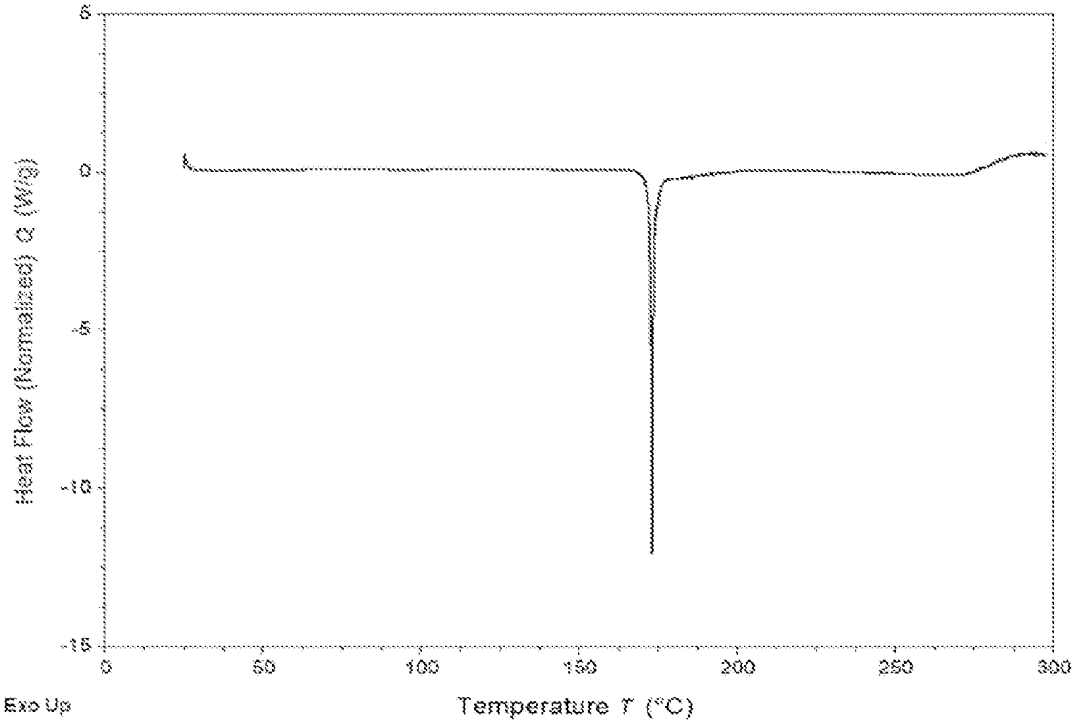

5
0
-5
-10
-15
Heat Flow (Normalized) Q (W/g)
0
50
100
150
200
250
300
Exo Up
Temperature T (°C)

FIG. 3

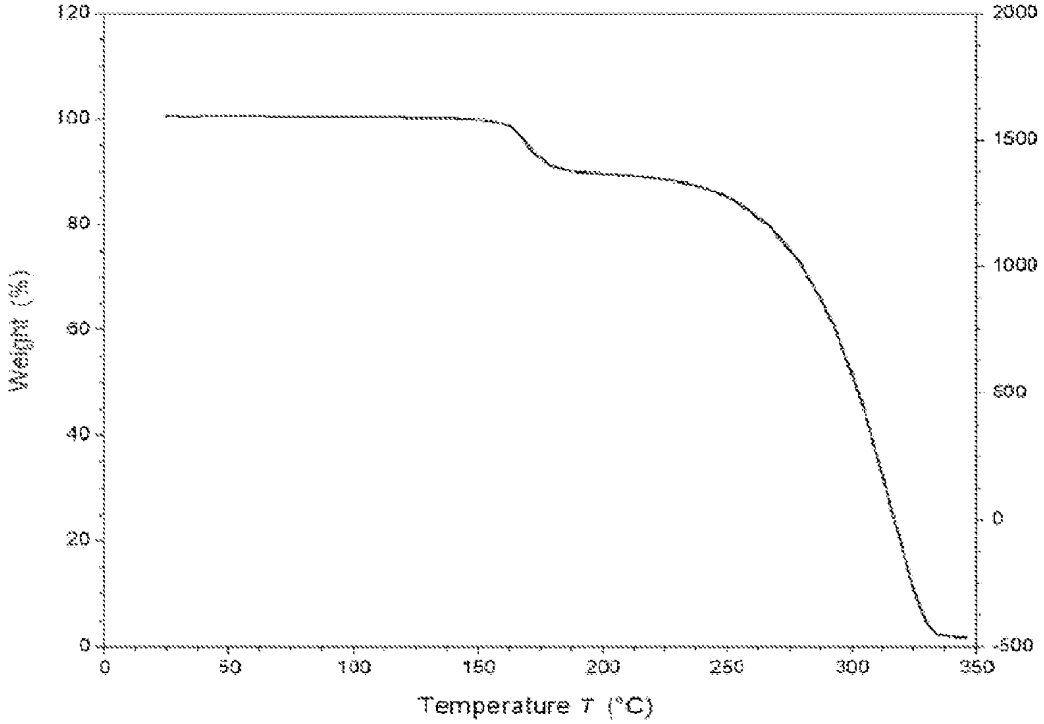

120
100
80
60
40
20
0
Weight (%)
2000
1500
1000
500
0
-500
0
50
100
150
200
250
300
350
Temperature T (°C)

FIG. 4

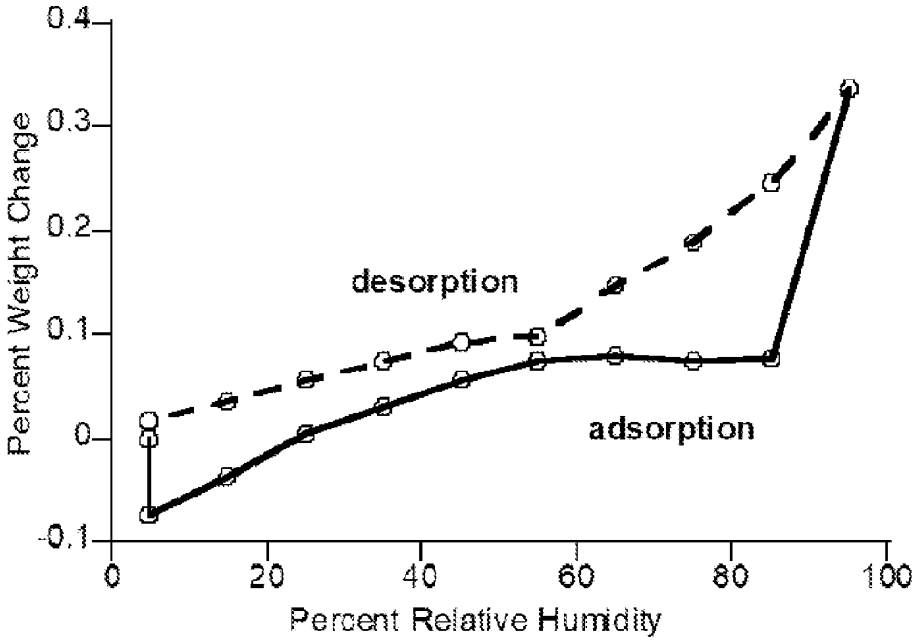

0.4
0.3
0.2
0.1
0
-0.1
Percent Weight Change
desorption
adsorption
0
20
40
60
80
100
Percent Relative Humidity

**FIG. 5**

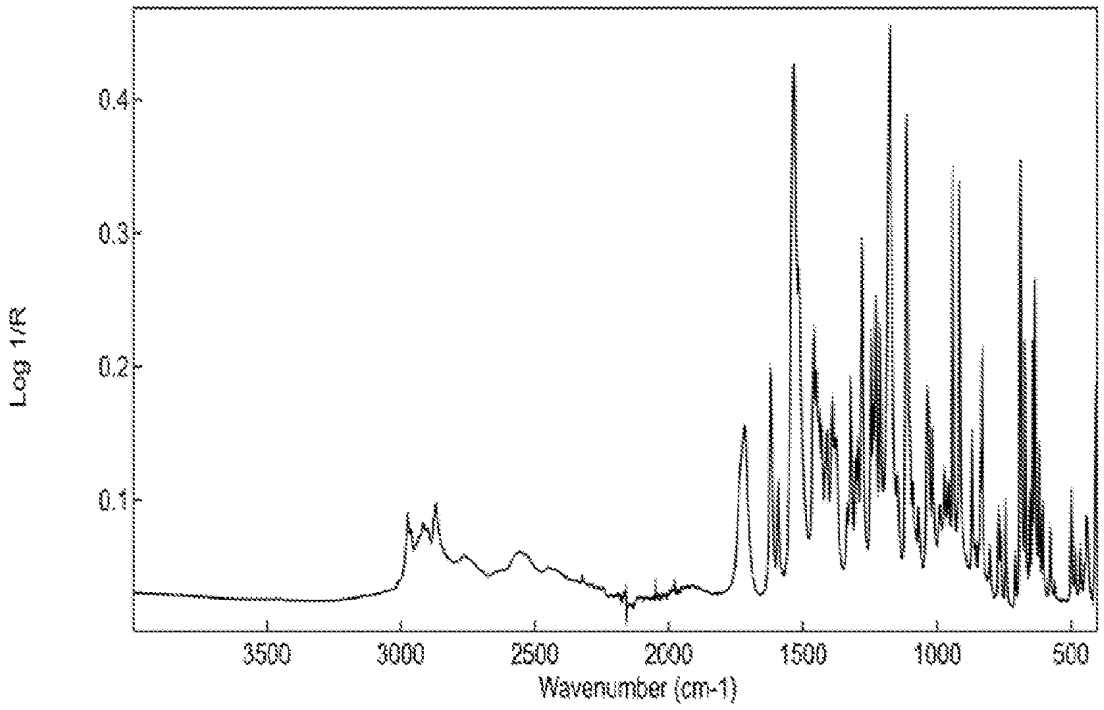

Log 1/R
0.4
0.3
0.2
0.1
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

**FIG. 6**

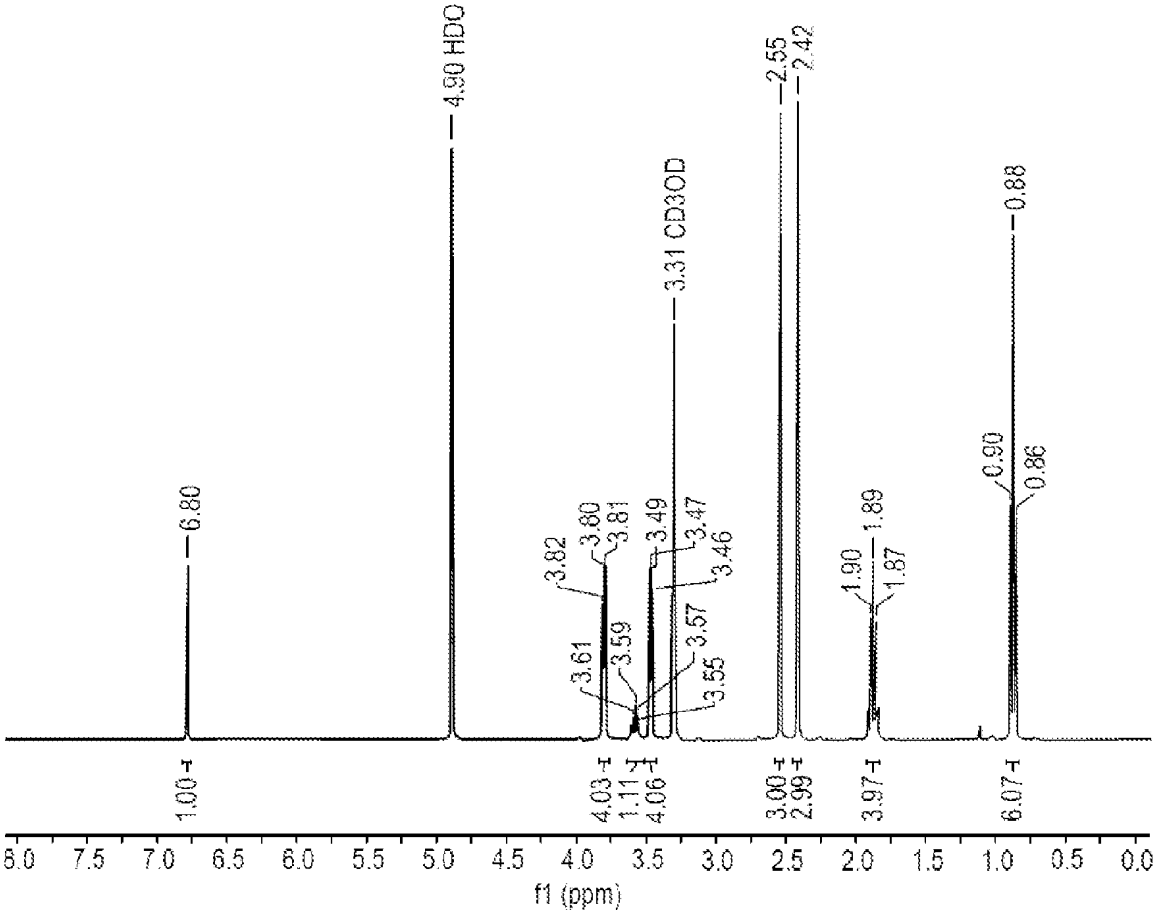
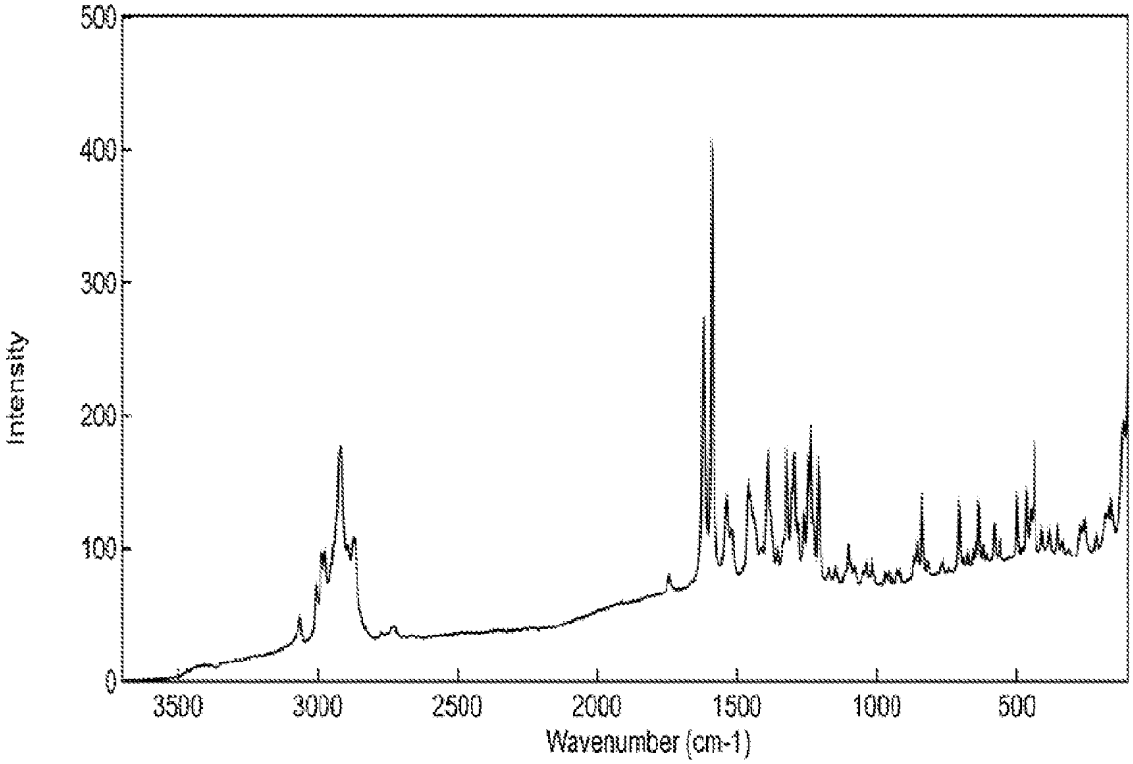

4.90 HDO
3.31 CD3OD
2.55
2.42
0.88
6.80
3.82
3.80
3.81
3.49
3.47
3.46
3.61
3.59
3.57
3.55
1.90
1.89
1.87
0.90
0.86
1.00
4.03
1.11
4.06
3.00
2.99
3.97
6.07
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

FIG. 7


500
400
300
200
100
0
Intensity
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/US2022/050436**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

**See Supplemental Box for Details**

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/US2022/050436**

A. CLASSIFICATION OF SUBJECT MATTER

***C07D 487/04 (2006.01) A61K 31/5377 (2006.01) A61K 47/12 (2006.01) A61K 9/00 (2006.01) A61P 5/38 (2006.01) A61P 15/08 (2006.01) A61P 5/24 (2006.01)***

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Google, EPOQUE and STN Search - PATENW, BIOSIS, CAPLUS, EMBASE, MEDLINE, REGISTRY; Keywords – tildacerfont, oxalic acid, corticotropin releasing factor, CRHR1, CRF1, congenital adrenal hyperplasia, CAH, and related terms

Applicant/Inventor Search - Espacenet, PubMED, AusPAT, Google Patents, IP Australia Internal Databases, REDDY, Dasharatha; RAJAGOPAL, Ashokraj; WANG, Lu; BARNES, Christopher; SPRUCE BIOSCIENCES, INC.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| | Documents are listed in the continuation of Box C | |

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 February 2023 | 20 February 2023 |

| **Name and mailing address of the ISA/AU** | **Authorised officer** |
|---|---|
| AUSTRALIAN PATENT OFFICE<br>PO BOX 200, WODEN ACT 2606, AUSTRALIA<br>Email address: pct@ipaustralia.gov.au | Anthony Lai<br>AUSTRALIAN PATENT OFFICE<br>(ISO 9001 Quality Certified Service)<br>Telephone No. +61 2 6283 2642 |

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2021016208 A1 (SPRUCE BIOSCIENCES, INC.) 28 January 2021<br>[0125]-[0126]; Examples 2-3 | 25-55 and 75-105 |
| X | US 2020/0255436 A1 (Spruce Biosciences, Inc.) 13 August 2020<br>Abstract; [0019]; Example 10-12, Table 12 and 15-16 | 25-55 and 75-105 |
| X | Sarafoglou K, Barnes CN, Huang M, Imel EA, Madu IJ, Merke DP, Moriarty D, Nakhle S, Newfield RS, Vogiatzi MG, Auchus RJ. Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies. J Clin Endocrinol Metab. 2021 Oct 21;106(11):e4666-e4679. doi: 10.1210/clinem/dgab438.<br>Abstract | 25-55 and 75-105 |
| X | WO 2008/036579 A1 (ELI LILLY AND COMPANY) 27 March 2008<br>Abstract; Example 16 | 25-55 and 75-105 |

## Supplemental Box

**Continuation** of: **Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1-24 and 56-74 (in full), and claims 75-105 (in part) are directed to compositions comprising a salt crystal form of tildacerfont, wherein the feature of the salt crystal form of tildacerfont is specific to this group of claims
- Claims 25-55 (in full), and claims 75-105 (in part) are directed to compositions comprising tildacerfont available in any form, wherein the feature of tildacerfont is specific to this group of claims

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions and which provides a technical relationship among them is tildacerfont

However it is considered that this feature is generic in this particular art. Therefore in this light this common feature cannot be a special technical feature. Hence there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied a *priori*.

| INTERNATIONAL SEARCH REPORT<br>Information on patent family members | International application No.<br>PCT/US2022/050436 |
|---|---|

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent Document/s Cited in Search Report | | Patent Family Member/s | |
|---|---|---|---|
| **Publication Number** | **Publication Date** | **Publication Number** | **Publication Date** |
| WO 2021016208 A1 | 28 January 2021 | WO 2021016208 A1 | 28 Jan 2021 |
| | | AR 119442 A1 | 15 Dec 2021 |
| | | AU 2020318970 A1 | 03 Mar 2022 |
| | | BR 112022000956 A2 | 05 Apr 2022 |
| | | CA 3147891 A1 | 28 Jan 2021 |
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| | | EP 3986416 A1 | 27 Apr 2022 |
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| | | KR 20090052366 A | 25 May 2009 |
| | | KR 101088239 B1 | 30 Nov 2011 |
| | | MA 30798 B1 | 01 Oct 2009 |

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

| INTERNATIONAL SEARCH REPORT<br>Information on patent family members | International application No.<br>**PCT/US2022/050436** |
|---|---|

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent Document/s Cited in Search Report | | Patent Family Member/s | |
|---|---|---|---|
| **Publication Number** | **Publication Date** | **Publication Number** | **Publication Date** |
| | | MX 2009003125 A | 28 May 2009 |
| | | MY 146388 A | 15 Aug 2012 |
| | | NZ 575572 A | 28 Oct 2011 |
| | | PE 20081377 A1 | 18 Sep 2008 |
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| | | TW 200821312 A | 16 May 2008 |
| | | TW I402269 B | 21 Jul 2013 |
| | | US 2010222339 A1 | 02 Sep 2010 |
| | | US 8030304 B2 | 04 Oct 2011 |

**End of Annex**

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 3 784 233 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
**05.06.2024 Bulletin 2024/23**

(21) Application number: **19793181.9**

(22) Date of filing: **26.04.2019**

(51) International Patent Classification (IPC):
***A61K 31/4162*** *(2006.01)* ***A61K 31/505*** *(2006.01)*
***A61K 31/519*** *(2006.01)* ***C07D 231/54*** *(2006.01)*
***C07D 233/70*** *(2006.01)* ***C07D 247/02*** *(2006.01)*
***A61K 9/20*** *(2006.01)* ***A61P 35/00*** *(2006.01)*

(52) Cooperative Patent Classification (CPC):
(C-Sets available)
**A61K 31/519; A61K 31/5377; A61K 45/06; A61P 35/00;** A61K 9/2004; A61K 9/4841 (Cont.)

(86) International application number:
**PCT/US2019/029486**

(87) International publication number:
**WO 2019/210266 (31.10.2019 Gazette 2019/44)**

(54) **METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS**

VERFAHREN ZUR BEHANDLUNG VON HODEN-UND EIERSTOCK-NEBENNIERENTUMOREN

MÉTHODES DE TRAITEMENT DE TUMEURS DES VERTIGES SURRÉNALIENS DES TESTICULES ET DES OVAIRES

(84) Designated Contracting States:
**AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(30) Priority: **27.04.2018 US 201862663951 P**
**23.03.2019 US 201962822815 P**

(43) Date of publication of application:
**03.03.2021 Bulletin 2021/09**

(73) Proprietor: **Spruce Biosciences, Inc.**
**South San Francisco, CA 94080 (US)**

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  **San Francisco, California 94115 (US)**
- **GERBER, Hal**
  **Boca Raton, Florida 33432 (US)**

(74) Representative: **Doherty, William et al**
**Albright IP Limited**
**County House**
**Bayshill Road**
**Cheltenham, Glos. GL50 3BA (GB)**

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**WO-A1-2019/036472** **WO-A1-2019/036503**
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**US-A1- 2017 020 877**

- **CHEN HUA-DONG ET AL: "Ovarian Adrenal Rest Tumors Undetected by Imaging Studies and Identified at Surgery in Three Females with Congenital Adrenal Hyperplasia Unresponsive to Increased Hormone Therapy Dosage", ENDOCRINE PATHOLOGY, HUMANA PRESS, TOTOWA, NJ, US, vol. 28, no. 2, 28 December 2016 (2016-12-28), pages 146-151, XP036564071, ISSN: 1046-3976, DOI: 10.1007/S12022-016-9461-4 [retrieved on 2016-12-28]**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

(52) Cooperative Patent Classification (CPC): (Cont.)

C-Sets
**A61K 31/5377, A61K 2300/00**

## Description

### CROSS-REFERENCE

**[0001]** This application claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed April 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019.

### BACKGROUND

**[0002]** Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

**[0003]** CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

**[0004]** Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, *inter alia*, are solutions to these and other problems in the art. Document CHEN HUA-DONG ET AL: "Ovarian Adrenal Rest Tumors Undetected by Imaging Studies and Identified at Surgery in Three Females with Congenital Adrenal Hyperplasia Unresponsive to Increased Hormone Therapy Dosage",ENDOCRINE PATHOLOGY, HUMANA PRESS, TOTOWA, NJ, US, vol. 28, no. 2, 28 December 2016 (2016-12-28), pages 146-151
discloses how patients with congenital adrenal hyperplasia have a predisposition for developing adrenal rest tumors. In contrast to testicular adrenal rest tumors, ovarian adrenal rest tumors are less common, and only a few cases have been reported in the literature. The preferred treatment for this type of tumors, which are also presently claimed, is said to be adrenal hormone replacement therapy.

### SUMMARY

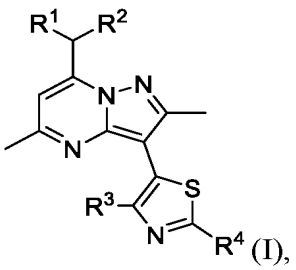
**[0005]** The references to methods of treatment in the summary and detailed description of the invention in this description are to be interpreted as references to the compounds, pharmaceutical compositions and medicaments of the present invention for use in a method for treatment of the human (or animal) body by therapy. Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

**[0006]** Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

**[0007]** One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

**[0008]** In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

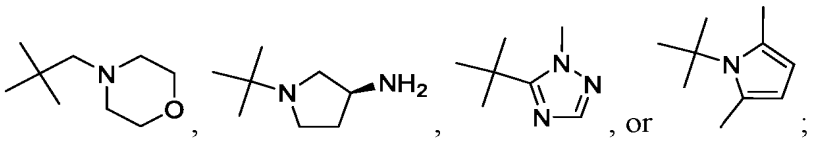
**[0009]** One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,
wherein:

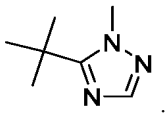
$R^1$ and $R^2$ are independently ethyl or n-propyl;
$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and
$R^4$ is hydrogen, Br, $R^aR^bN$-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



;

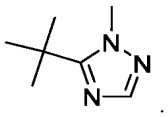
$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-.

**[0010]** In some embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl. In some embodiments, $R^3$ is Cl, Br, or methyl. In some embodiments, $R^4$ is Br, $R^aR^bN$-, pyridin-4-yl, morpholin-4-yl, or



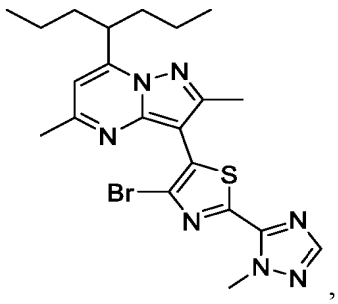
.

In some embodiments, $R^4$ is morpholin-4-yl or



.

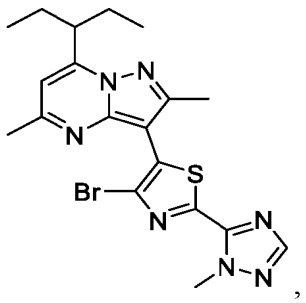
**[0011]** In some embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$- and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl. In some embodiments, the compound is



,

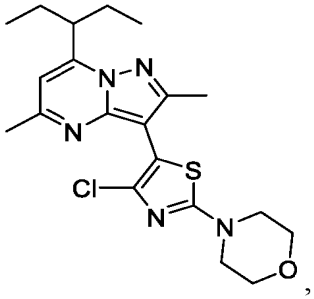
or a pharmaceutically acceptable salt thereof.

**[0012]** In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

**[0013]** In some embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

**[0014]** In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

**[0015]** In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

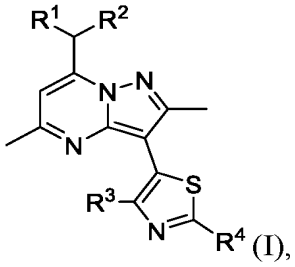
**[0016]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

**[0017]** In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

**[0018]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically

acceptable salt thereof, is administered at about 10 pm at night.

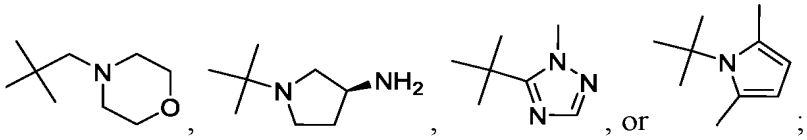
**[0019]** One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:



(I),

or a pharmaceutically acceptable salt thereof,
wherein:

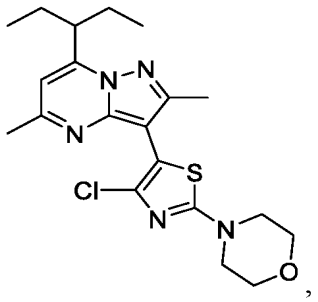
$R^1$ and $R^2$ are independently ethyl or n-propyl;
$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and
$R^4$ is hydrogen, Br, $R^aR^bN$-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



;

$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-.

**[0020]** In some embodiments, the compound of Formula (I) has the structure:



,

or a pharmaceutically acceptable salt thereof.

**[0021]** In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0022]** In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about

295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

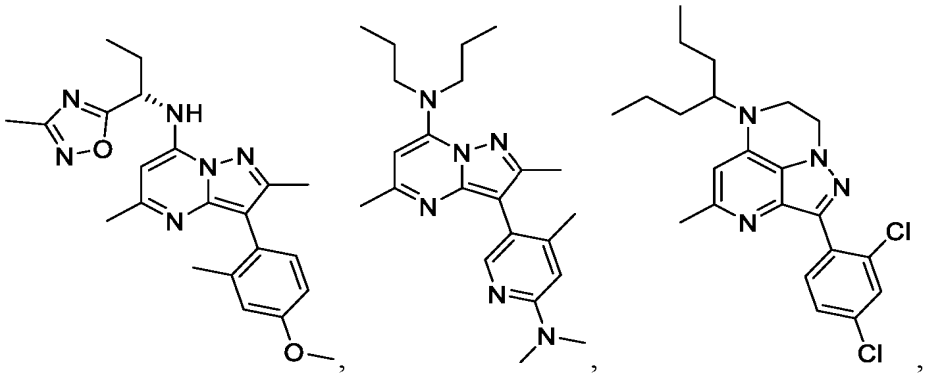
**[0023]** In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

**[0024]** In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

**[0025]** In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

**[0026]** In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

**[0027]** In some embodiments, the additional chemotherapeutic agent is another $CRF_1$ antagonist. In some embodiments, the $CRF_1$ antagonist is



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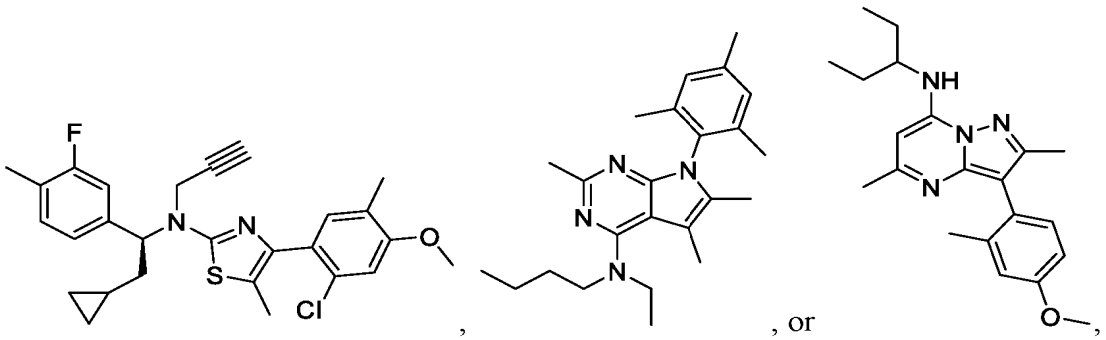
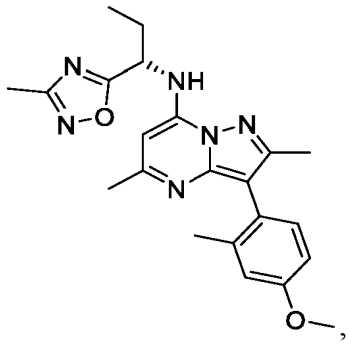


or a pharmaceutically acceptable salt thereof.

**[0028]** In some embodiments, the $CRF_1$ antagonist is



or a pharmaceutically acceptable salt thereof.

**[0029]** In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

**[0030]** In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

**[0031]** In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0032]** In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural

**[0033]** Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the $CRF_1$ antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0034]** In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0035]** Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. Accordingly, the drawings and description are to be regarded as illustrative.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0036]** The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

**FIG. 1A-1B.** A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics **(A)**. A schematic representation of inhibition of $CRF_1$ with a $CRF_1$ antagonist (Compound 1) **(B)**.

**FIG. 2**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a $CRF_1$ antagonist (Compound 1).

**FIG. 3**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a $CRF_1$ antagonist (Compound 1).

**FIG. 4**. Graphic representation of patient-level response (measuring ACTH levels) to a $CRF_1$ antagonist (Compound 1).

**FIG. 5A-5B.** Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a $CRF_1$ antagonist [Subject 003001 **(A)**; Subject 007002 **(B)**].

**FIG. 6**. Graphic representation of patient-level response (measuring 17-OHP levels) to a $CRF_1$ antagonist (Compound 1).

**FIG. 7A-7B**. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to

a $CRF_1$ antagonist [Subject 003001 **(A)**; Subject 007002 **(B)**].

**FIG. 8**. Graphic representation of patient-level response (measuring androstenedione levels) to a $CRF_1$ antagonist (Compound 1).

**FIG. 9A-9B.** Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a $CRF_1$ antagonist (Compound 1) [Subject 003001 **(A)**; Subject 007002 **(B)**].

**FIG. 10A-10B.** Images of a patient with TART pre-treatment with a $CRF_1$ antagonist (Compound 1) **(A)** and 6-weeks post-treatment with a $CRF_1$ antagonist (Compound 1) **(B)**.

**FIG. 11A-11B.** Graphic representation of an *in vitro* binding assay of a $CRF_1$ antagonist (Compound 1); $^{125}$I-sauvagine binding to rat cerebellar membranes one hour after oral administration of increasing Compound 1 doses **(A)** and *in vivo* inhibition of CRF-induced activity after treatment with a $CRF_1$ antagonist; Compound 1 (oral, 10 mg/kg) **(B)**.

**FIG. 12A-12B.** Graphic representation of ACTH levels **(A)** and 17-OHP levels **(B)** after treatment with a $CRF_1$ antagonist (Compound 1).

**FIG. 13**. Graphic representation of hormone responses after treatment with a $CRF_1$ antagonist (Compound 1).

**FIG. 14** depicts the proof of concept and escalating QD dosing at 10 pm.

**FIG. 15A-15D** are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

**FIG. 16A-16D** are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

**FIG. 17A-17D** are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

## DETAILED DESCRIPTION

**[0037]** While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only.

### I. Definitions

**[0038]** The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

**[0039]** Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

**[0040]** The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., $C_1$-$C_{10}$ means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

**[0041]** The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

**[0042]** The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be

consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

**[0043]** Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as - C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

**[0044]** The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

**[0045]** The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo($C_1$-$C_4$)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

**[0046]** The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

**[0047]** The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

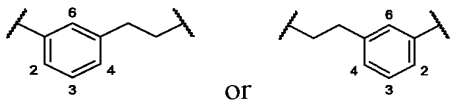
**[0048]** Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual

rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

**[0049]** The symbol "" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

**[0050]** The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

**[0051]** The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:




**[0052]** An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -CHO, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2CH_3$ $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, substituted or unsubstituted $C_1$-$C_5$ alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

**[0053]** Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

**[0054]** Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R‴, -OC(O)R', - C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R‴, $-NR"C(O)_2R'$, - NR-C(NR'R"R‴)=NR"", -NR-C(NR'R")=NR‴, -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -NR'NR"R‴, -ONR'R", -NR'C(O)NR"NR‴R"", -CN, $-NO_2$, $-NR'SO_2R"$, -NR'C(O)R", - NR'C(O)-OR", -NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R‴, and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R‴, and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

**[0055]** Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, - SiR'R"R‴, -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R‴, $-NR"C(O)_2R'$, -NR-C(NR'R"R‴)=NR"", -NR-C(NR'R")=NR‴, -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -NR'NR"R‴, -ONR'R", -NR'C(O)NR"NR‴R"", -CN, $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro($C_1$-$C_4$)alkoxy, and fluoro($C_1$-$C_4$)alkyl, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R‴, and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R‴, and R"" groups when more than one of these

groups is present.

**[0056]** Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

**[0057]** Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

**[0058]** Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula $-T-C(O)-(CRR')_q-U-$, wherein T and U are independently -NR-, -O-, - CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, $-S(O)_2-$, $-S(O)_2NR'-$, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C"R"R'")_d-$, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituents R, R', R", and R‴ are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

**[0059]** As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

**[0060]** A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC= (O)H, - NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, un-

substituted aryl, unsubstituted heteroaryl, and
(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo,
halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC=(O)$NHNH_2$, -NHC=(O) $NH_2$, $-NHSO_2H$, -NHC= (O)H, - NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

**[0061]** A "size-limited substituent" or " size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_{20}$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_8$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

**[0062]** A "lower substituent" or " lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_8$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

**[0063]** In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

**[0064]** In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted $C_1$-$C_{20}$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_8$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted $C_1$-$C_{20}$ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted $C_3$-$C_8$ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted $C_6$-$C_{10}$ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

**[0065]** In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_8$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted $C_1$-$C_8$ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted $C_3$-$C_7$ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted $C_6$-$C_{10}$ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

**[0066]** Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to

include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

**[0067]** As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

**[0068]** The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

**[0069]** It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

**[0070]** Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

**[0071]** Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by $^{13}C$- or $^{14}C$-enriched carbon are within the scope of this invention.

**[0072]** The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium ($^{3}H$), iodine-125 ($^{125}I$), or carbon-14 ($^{14}C$). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

**[0073]** It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

**[0074]** "Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

**[0075]** The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted $C_1$-$C_{20}$ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted $C_1$-$C_{20}$ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

**[0076]** Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple $R^{13}$ substituents are present, each $R^{13}$ substituent may be distinguished as $R^{13A}$, $R^{13B}$, $R^{13C}$, $R^{13D}$, etc., wherein each of $R^{13A}$, $R^{13B}$, $R^{13C}$, $R^{13D}$, etc. is defined within the scope of the definition of $R^{13}$ and optionally differently.

**[0077]** A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

**[0078]** Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

**[0079]** The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared

with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see,* for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

**[0080]** Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

**[0081]** The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

**[0082]** In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

**[0083]** Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

**[0084]** "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of a compound to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

**[0085]** The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

**[0086]** A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

**[0087]** The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino

acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and "protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

**[0088]** A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, *e.g.,* in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

**[0089]** "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

**[0090]** The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

**[0091]** As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

**[0092]** The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist. In embodiments, an agonist is a molecule that interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

**[0093]** As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

**[0094]** The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

**[0095]** The terms "corticotropin-releasing factor type-1," "$CRF_1$," "corticotropin-releasing hormone receptor 1," and

"CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms include any recombinant or naturally-occurring form of $CRF_1$ variants thereof that maintain $CRF_1$ activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of $CRF_1$ variants (e.g., frameshift mutations) thereof that maintain $CRF_1$ activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype $CRF_1$). In embodiments, the $CRF_1$ protein encoded by the *CRHR1* gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

**[0096]** The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.).*

**[0097]** The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

**[0098]** As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

**[0099]** The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

**[0100]** "Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

**[0101]** "Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

**[0102]** The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leuke-

mia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

**[0103]** The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

**[0104]** The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

**[0105]** The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

**[0106]** The terms "treating" or "treatment" refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing In embodiments, treating does not include preventing.

**[0107]** "Treating" or "treatment" as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical

results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (*e.g.*, ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

**[0108]** "Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

**[0109]** The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

**[0110]** "Patient" or "subject in need thereof' refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

**[0111]** An "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.*, Lieberman, Pharmaceutical Dosage Forms (vols. 1-3, 1992); Lloyd, The Art, Science and Technology of Pharmaceutical Compounding (1999); Pickar, Dosage Calculations (1999); and Remington: The Science and Practice of Pharmacy, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a CRF1 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

**[0112]** For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

**[0113]** Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

**[0114]** The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

**[0115]** The terms "QD," "qd," and "q.d." refer to once a day, i.e., a drug or therapeutic agent is administered once a day for the duration of the therapeutic regimen.

**[0116]** The terms "BD," "bd," and "b.i.d." refer to twice a day, i.e., a drug or therapeutic agent is administered two times a day for the duration of the therapeutic regimen.

**[0117]** The terms "QID," "qid," and "q.i.d." refer to three times a day, i.e., a drug or therapeutic agent is administered three times a day for the duration of the therapeutic regimen.

**[0118]** Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

**[0119]** As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.,* a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, J. Biomater Sci. Polym. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao Pharm. Res. 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, J. Pharm. Pharmacol. 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.,* Al-Muhammed, J. Microencapsul. 13:293-306, 1996; Chonn, Curr. Opin. Biotechnol. 6:698-708, 1995; Ostro, Am. J. Hosp. Pharm. 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

**[0120]** By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions,

emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

**[0121]** For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

**[0122]** Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

**[0123]** The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

**[0124]** In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

**[0125]** The compounds described herein can be administered to treat a fertility disease or disorder and/or cancer. In this regard, the compounds disclosed herein may be administered either alone to treat such diseases or disorders or may be co-administered with another therapeutic agent to treat such diseases or disorders.

**[0126]** The compounds disclosed herein may be co-administered with an agonist or antagonist of $CRF_1$ function. The compounds described herein can be co-administered with conventional anti-cancer/chemotherapeutic.

**[0127]** "Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (*e.g.*, cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (*e.g.*, 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (*e.g.*, vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.),* topoisomerase inhibitors (*e.g.,* irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.,* doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins;

benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-aminotriazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflomithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bize-

lesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflomithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including recombinant interleukin II, or rIL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guérin (BCG), levam-

isole, interleukin-2, alpha-interferon, *etc.),* monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to $^{111}$In, $^{90}$Y, or $^{131}$I, *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa ™), erlotinib (Tarceva ™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

**[0128]** "Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

**[0129]** The compounds disclosed herein may be co-administered with an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5.alpha.-reductase such as finasteride; (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoli- n-4-amine (gefitinib, AZD 1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazoli- n-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family; (v) an anti angiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin .alpha.v.beta.3 function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme prodrug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

**[0130]** In embodiments, the compounds disclosed herein can be co-administered with an antibody, such as a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax 11-15) or antibody modulating Ig function such as anti-IgE (for example omalizumab).

**[0131]** In embodiments, treatment of cancer includes administration of an effective amount of at least two of the following: a CRF1 inhibitor, an inhibitor of the PD-L1/PD-1 pathway, an inhibitor of CTLA-4, an agonistic antibody of CD137 (4-1BB). In some embodiments, the method may comprise the use of two or more combinations.

**[0132]** In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as $^{47}$Sc, $^{64}$Cu, $^{67}$Cu, $^{89}$Sr, $^{86}$Y, $^{87}$Y, $^{90}$Y, $^{105}$Rh, $^{111}$Ag,

$^{111}In$, $^{117m}Sn$, $^{149}Pm$, $^{153}Sm$, $^{166}Ho$, $^{177}Lu$, $^{186}Re$, $^{188}Re$, $^{211}At$, and $^{212}Bi$, optionally conjugated to antibodies directed against tumor antigens.

**[0133]** In addition, a $CRF_1$ inhibitor may be combined with the therapeutic administration of immune cells, sometimes referred to as adoptive cell transfer. These cells may be cells from the patient, a genetically related or unrelated donor, they may be genetically modified (e.g. CAR-T cells, NK cells, etc), cell lines, genetically modified cell lines and live or dead versions of the above. CRF1 inhibitors may also be combined with vaccines of any kind (e.g. protein/peptide, viral, bacterial, cellular) to stimulate immune responses to cancer.

**[0134]** The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

**[0135]** The $CRF_1$ inhibitors/CRF, antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

**[0136]** The $CRF_1$ inhibitors/CRF, antagonists disclosed herein may be administered once daily until study reached endpoint. The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein may be administered at least three times but in some studies four or more times depending on the length of the study and/or the design of the study.

**[0137]** The compositions disclosed herein may be used in combination with additional cancer therapy. In some embodiments, the distinct cancer therapy comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy. In some embodiments, the cancer is a chemotherapy-resistant or radio-resistant cancer.

**[0138]** A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaroytic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (e.g., spodoptera) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

**[0139]** "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

**[0140]** The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. In some embodiments, a $CRF_1$ associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with $CRF_1$ (e.g. an endocrine disorder, a cancer including but not limited to TART or OART). A $CRF_1$ modulator is a compound that increases or decreases the activity or function or level of activity or level of function of $CRF_1$. A modulator may act alone, or it may use a cofactor, e.g., a protein, metal ion, or small molecule. Examples of modulators include small molecule compounds and other bioorganic molecules. Numerous libraries of small molecule compounds (e.g., combinatorial libraries) are commercially available and can serve as a starting point for identifying a modulator. The skilled artisan is able to develop one or more assays (e.g., biochemical or cell-based assays) in which such compound libraries can be screened in order to identify one or more compounds having the desired properties; thereafter, the skilled medicinal chemist is able to optimize such one or more compounds by, for example, synthesizing and evaluating analogs and derivatives thereof. Synthetic and/or molecular modeling studies can also be utilized in the identification of an activator.

**[0141]** The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms "modulate", "modulation" and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of $CRF_1$, either directly or indirectly, relative to the absence of the molecule.

**[0142]** The term "associated" or "associated with" in the context of a substance or substance activity or function

associated with a disease (e.g. a protein associated disease, an endocrine disorder, a disease associated with $CRF_1$ activity, a $CRF_1$ associated disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, an endocrine disorder associated with $CRF_1$ activity or function may be an endocrine disorder that results (entirely or partially) from aberrant $CRF_1$ function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or an endocrine disorder wherein a particular symptom of the disease is caused (entirely or partially) by aberrant $CRF_1$ activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, an endocrine disorder associated with $CRF_1$ activity or function or a $CRF_1$ associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., $CRF_1$ modulator, $CRF_1$ inhibitor, or $CRF_1$ antagonist), in the instance where increased $CRF_1$ activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART). For example, an endocrine disorder associated with $CRF_1$ activity or function or a $CRF_1$ associated endocrine disorder, may be treated with an $CRF_1$ modulator or $CRF_1$ inhibitor, in the instance where increased $CRF_1$ activity or function (e.g. signaling pathway activity) causes the disease.

**[0143]** The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

**[0144]** The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propogated to other signaling pathway components. For example, binding of a $CRF_1$ with a compound as described herein may reduce the level of a product of the $CRF_1$ catalyzed reaction or the level of a downstream derivative of the product or binding may reduce the interactions between the $CRF_1$ or a reaction product and downstream effectors or signaling pathway components (e.g., MAP kinase pathway), resulting in changes in cell growth, proliferation, or survival.

**[0145]** As used herein, the terms "corticotropin-releasing factor type-1," "$CRF_1$," "corticotropin-releasing hormone receptor 1," and "CHHR1" and all other related art-accepted terms, many of which are set forth below, refer to a compound capable of modulating, either directly or indirectly, the $CRF_1$ receptor in an *in vitro* assay, an *in vivo* model, and/or other means indicative of therapeutic efficacy. The terms also refer to a compound that exhibits at least some therapeutic benefit in a human subject.

**[0146]** The phrase "in a sufficient amount to effect a change" means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject's feeling of well-being).

**[0147]** The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

**[0148]** "Substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

**[0149]** The terms "specifically binds" and "selectively binds," when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample. The antibody, or binding composition derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen, or a variant or mutein thereof, with an affinity that is at least two-fold greater, at least 10-times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antibody, or binding composition derived therefrom. In embodiments, the antibody will have an affinity that is greater than about $10^9$ liters/mol, as determined by, e.g., Scatchard analysis (Munsen, et al. (1980) Analyt. Biochem. 107:220-239).

**[0150]** The terms "DNA," "nucleic acid," "nucleic acid molecule," "polynucleotide" and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, messenger RNA (mRNA),

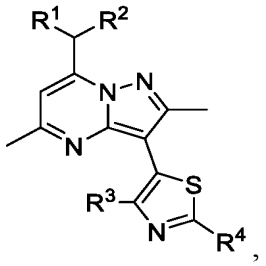
complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

**[0151]** As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced (e.g., muteins); for example, the change is generated in the laboratory by human intervention ("hand of man"). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

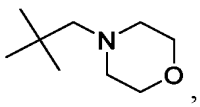
**[0152]** The term "muteins" as used herein refers broadly to mutated recombinant proteins. These proteins usually carry single or multiple amino acid substitutions and are frequently derived from cloned genes that have been subjected to site-directed or random mutagenesis, or from completely synthetic genes.

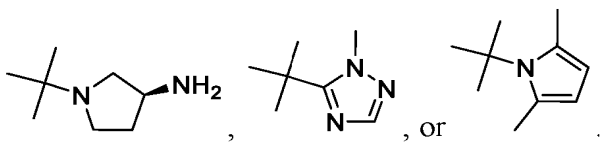
## II. Compounds

**[0153]** In an aspect provided herein, is a compound of Formula (I):



or a pharmaceutically acceptable salt thereof. $R^1$ and $R^2$ are independently ethyl or n-propyl. $R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. $R^4$ is hydrogen, Br, $R^aR^bN$-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



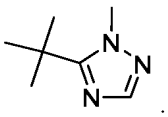


$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-In embodiments, the inhibitor forms an irreversible bond with the amino acid residue. In embodiments, the bond is a covalent bond.

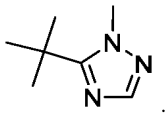
**[0154]** In certain embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl.

**[0155]** In certain embodiments, $R^3$ is Cl, Br, or methyl.

**[0156]** In certain embodiments, $R^4$ is Br, $R^aR^bN$-, pyridin-4-yl, morpholin-4-yl, or

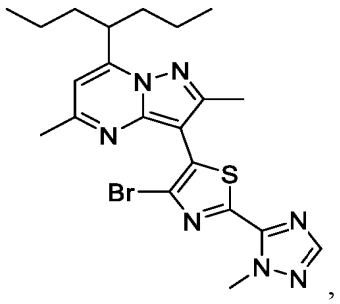


**[0157]** In certain embodiments, $R^4$ is morpholin-4-yl or



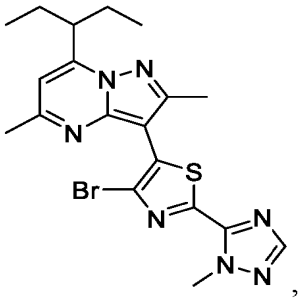
**[0158]** In certain embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$- and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

**[0159]** In certain embodiments, the compound is



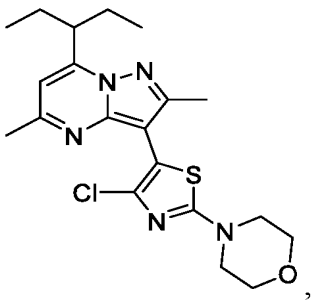
or a pharmaceutically acceptable salt thereof.

**[0160]** In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

**[0161]** In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

**[0162]** The invention is defined by the claims. Any subject-matter falling outside the scope of the claims is provided for information purposes only. The following paragraphs are part of the disclosure but are not claimed.

**[0163]** In one aspect described herein, there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

**[0164]** In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof; and repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of said astressin.

**[0165]** In one aspect described herein, there is a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

**[0166]** In one aspect described herein, there is a method of improving quality of life in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

### III. Pharmaceutical Compositions

**[0167]** In an aspect, there is provided a pharmaceutical composition, for the claimed use, including a compound as described herein, including embodiments, or the structural Formula (I), and a pharmaceutically acceptable excipient.

**[0168]** The compounds (e.g., $CRF_1$ inhibitors/antagonists) of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are "pharmaceutical compositions" comprising a compound (e.g., $CRF_1$ inhibitor(s)/ antagonist(s)) and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In certain embodiments, the compound (e.g., $CRF_1$ inhibitor/antagonist) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

**[0169]** In one aspect described herein, there is a pharmaceutical composition in the form of a capsule comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a pharmaceutical composition in the form of a tablet comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

**[0170]** The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

**[0171]** The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of $CRF_1$ function) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

**[0172]** The tablets, capsules and the like suitable for oral administration may be uncoated or coated to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered compo-

sition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly(methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

**[0173]** Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

**[0174]** Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

**[0175]** Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

**[0176]** Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

**[0177]** The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

**[0178]** The pharmaceutical compositions typically comprise a therapeutically effective amount of a $CRF_1$ inhibitor/antagonist contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

**[0179]** After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

**[0180]** Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a $CRF_1$ inhibitor/antag-

onist, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

**[0181]** Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., $CRF_1$ inhibitor/antagonist) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

**[0182]** The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

**[0183]** The present disclosure contemplates the administration of the compound (e.g., $CRF_1$ inhibitor/antagonist) in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

**[0184]** The compound (e.g., $CRF_1$ inhibitor/antagonist) contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

## IV. Methods

**[0185]** In certain embodiments, provided herein are methods for treating or preventing a disease comprising administering an effective amount of a compound of Formula (I), or an isotopic variant thereof or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

**[0186]** In one embodiment, provided herein are methods for treating or preventing a tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a benign tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a malignant tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal rest tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

**[0187]** In one embodiment, provided herein are methods for treating or preventing infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing male infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm count, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm motility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm morphology, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing female infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

**[0188]** In one embodiment, provided herein are methods for treating or preventing a proliferative or hyperproliferative disease or disorder according to the claims, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, thereof. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a cancer of the breast, skin, prostate, cervix, uterus, ovary,

testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system.

**[0189]** In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenstrom's macroglobulinernia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, aligodendrogliorna, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mutinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prol actin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonserninoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but not limited to, renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (*See* Fishman et al., 1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy et al., 1997, Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

**[0190]** Depending on the disorder, disease, or condition to be treated, and the subject's condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal,

intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration as described elsewhere herein.

**[0191]** The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. Recommended routes of administration for the second active agents are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

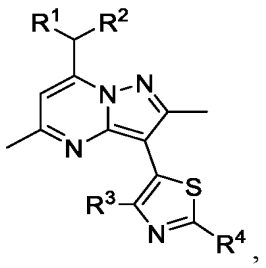
**[0192]** In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

**[0193]** In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

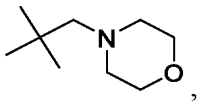
**[0194]** In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

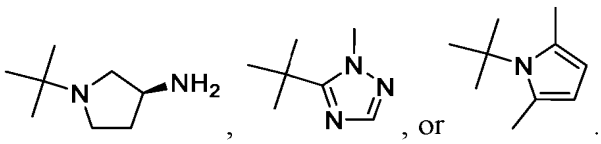
**[0195]** In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

**[0196]** In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):



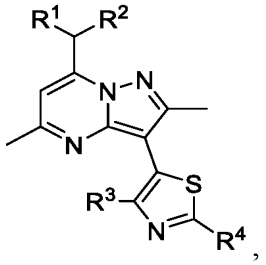
or a pharmaceutically acceptable salt thereof. $R^1$ and $R^2$ are independently ethyl or n-propyl. $R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. $R^4$ is hydrogen, Br, $R^aR^bN$-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,





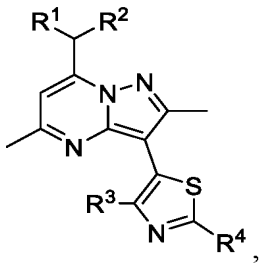
$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-.

**[0197]** In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments.

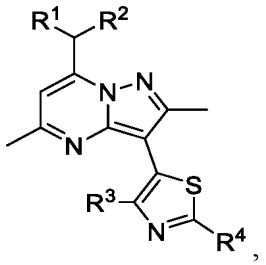
**[0198]** In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and R are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 60% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 70% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 80% of the subjects demonstrate reduction in ACTH. In embodiments, at least about 10% of subjects were in the standard or normal range for ACTH after treatment.

**[0199]** In embodiments, at least about 20% of subjects were in the standard or normal range for ACTH after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for ACTH after treatment. In certain embodiments, ACTH levels are decreased or reduced within about 30 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 1 hour post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

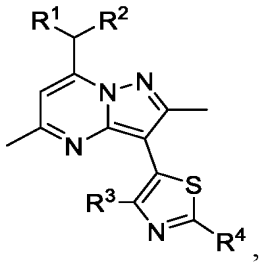
**[0200]** In an aspect provided herein, is a method of decreasing or reducing 17$\alpha$-hydroxyprogesterone (17-OHP) levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 60% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 70% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 80% of the subjects demonstrate reduction in 17-OHP. In embodiments, at least

about 30% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 60% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 60% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment.

**[0201]** In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

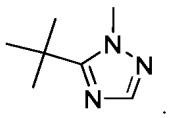


or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 60% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 70% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 80% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 90% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least 100% of the subjects demonstrate reduction in androstenedione. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least 60% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range for androstenedione after treatment.

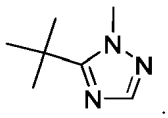
**[0202]** In certain embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl.

**[0203]** In certain embodiments, $R^3$ is Cl, Br, or methyl.

**[0204]** In certain embodiments, $R^4$ is Br, $R^aR^bN$-, pyridin-4-yl, morpholin-4-yl, or

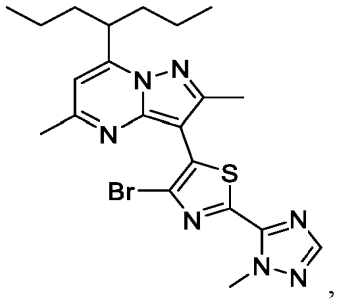


**[0205]** In certain embodiments, $R^4$ is morpholin-4-yl or



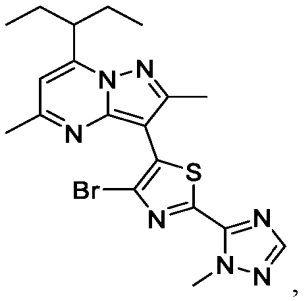
**[0206]** In certain embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$- and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

**[0207]** In certain embodiments, the compound is



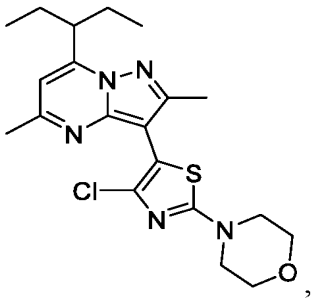
or a pharmaceutically acceptable salt thereof.

**[0208]** In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

**[0209]** In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

**[0210]** In certain embodiments, a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate thereof is cyclically administered to a patient. Cycling therapy involves the administration of an active agent or a combination of active agents for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment. Prodrugs of the present compounds are not part of the claimed invention.

**[0211]** In certain embodiments, in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein (e.g., treatment or prevention of testicular adrenal rest tumors (TART) or treatment or prevention of ovarian adrenal rest tumors (OART)), an appropriate dosage level of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof generally is ranging from about 1 mg to 3000 mg, from about 1 mg to 2000 mg, from about 1 mg to 1000 mg, from about 1 mg to about 500 mg, from about 5 mg to about 500 mg, from about 5 mg to about 400 mg, from about 5 mg to about 300 mg, from about 5 mg to about 250 mg, from about 5 mg to about 200 mg, from about 50 mg to about 200 mg, from about 10 mg to about 400 mg, from about 5 mg to about 25 mg, from about 10 mg to about 25 mg, or from about 25 to about 200 mg, which can be administered in single or multiple doses. In certain embodiments, the compound of Formula (I),

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg/day.

**[0212]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg.

**[0213]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, or about 1000 mg.

**[0214]** For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing from about 1.0 mg to about 1,000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about

680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof for the symptomatic adjustment of the dosage to the patient to be treated. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 50 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 200 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.The pharmaceutical compositions can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about

305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered three times per day.

**[0215]** In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate thereof is administered for a period of one day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of two days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of three days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of four days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of five days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of six days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of seven days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of eight days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of nine days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of ten days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 11 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 12 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 13 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 14 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 15 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 16 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 17 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 18 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 19 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 20 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 21 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 22 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 23 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 24 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 25 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate,

hydrate, or prodrug thereof is administered over a period of 26 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 27 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 28 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 29 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 30 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 31 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 32 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 33 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 34 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 35 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 36 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 37 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 38 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 39 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 40 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 41 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 42 days or more.

**[0216]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days.

**[0217]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or

prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 14 days.

**[0218]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or

prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to

at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 14 days.

**[0219]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 28 days. In

certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 28 days.

**[0220]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a phar-

maceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 28 days.

**[0221]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 255 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or

a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily

for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 42 days.

**[0222]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of

Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 42 days.

**[0223]** In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, or about 800 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered at least once per day.

**[0224]** In certain embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subj ect.

**[0225]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

**[0226]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formu-

lated as a capsule or tablet.

**[0227]** In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

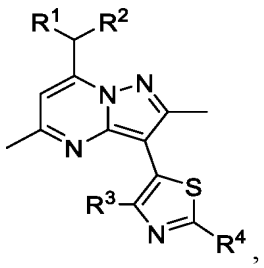
**[0228]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject.In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day.

**[0229]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

**[0230]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 6 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 5 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 3 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 1 hour before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

**[0231]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

**[0232]** In another aspect is provided a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I): and a pharmaceutically acceptable excipientcomprising with a compound as described herein, including embodiments, or the structural Formulae (I) and a pharmaceutically acceptable excipient:



or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$, and $R^4$ are as described herein, including embodiments.

**[0233]** In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0234]** In certain embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about

270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0235]** In certain embodiments, the pharmaceutical composition is administered orally.

**[0236]** In certain embodiments, the pharmaceutical composition is formulated as a capsule or tablet. In certain embodiments, the capsule or tablet comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 50 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 200 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0237]** In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subj ect.

**[0238]** In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

**[0239]** In certain embodiments, the pharmaceutical composition is administered in the fed state. In certain embodiments, the pharmaceutical composition is administered in the fasted state. In certain embodiments, the pharmaceutical composition is administered at least once per day.

**[0240]** In certain embodiments, the pharmaceutical composition is administered at bedtime. In certain embodiments, the pharmaceutical composition is administered less than about 6 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 5 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 3 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 1 hour before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep.

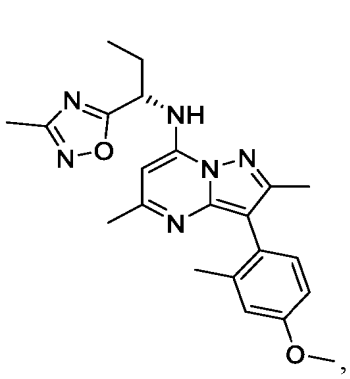
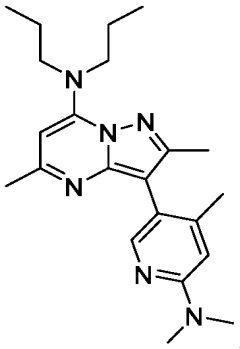
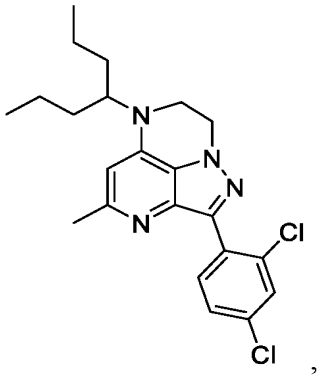
**[0241]** In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

**[0242]** In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

**[0243]** In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

**[0244]** In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

**[0245]** In certain embodiments, the the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In certain embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In certain embodiments, the mineralocorticoid is fludrocortisone. In certain embodiments, the additional chemotherapeutic agent is another $CRF_1$ antagonist. In certain embodiments, the $CRF_1$ antagonist is:

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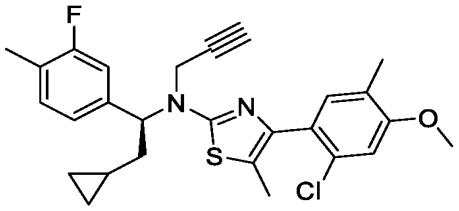
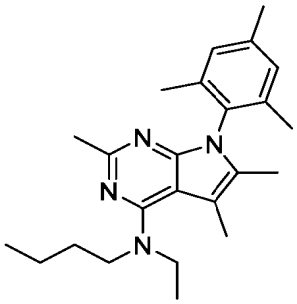
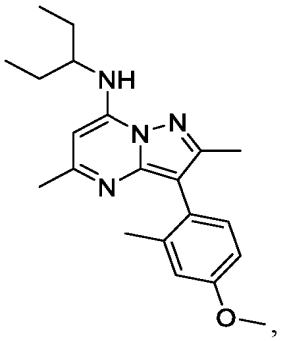
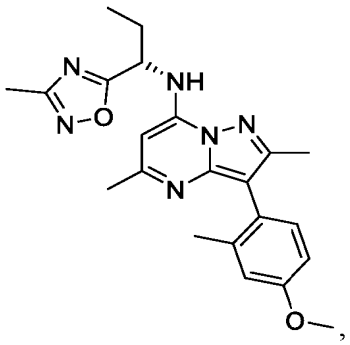




or a pharmaceutically acceptable salt thereof. In certain embodiments, the $CRF_1$ antagonist is



or a pharmaceutically acceptable salt thereof.

**[0246]** In certain embodiments of the methods disclosed herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In certain embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0247]** In certain embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the radiation therapy

is prior to administration of the $CRF_1$ antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0248]** In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. In some embodiments, a tablet comprises a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil, or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. In some embodiments, a capsule comprises a solid carrier such as gelatin.

**[0249]** In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer's injection, or Lactated Ringer's injection. In some embodiments, preservatives, stabilisers, buffers, antioxidants, and/or other additives are included as required.

**[0250]** In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

**[0251]** The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy,* supra; Modified-Release Drug Delivery Technology, 2nd Edition, Rathbone et al., Eds., Marcel Dekker, Inc.: New York, NY, 2008).

**[0252]** The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

**[0253]** The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

**[0254]** In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

**[0255]** The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

**[0256]** Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression.

Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

**[0257]** Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

**[0258]** Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

**[0259]** Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

**[0260]** Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

**[0261]** It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

**[0262]** The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that

resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

**[0263]** The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

**[0264]** The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

**[0265]** Coloring and flavoring agents can be used in all of the above dosage forms.

**[0266]** The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

**[0267]** The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

**[0268]** The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy,* supra).

**[0269]** The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

**[0270]** Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*'-methy1-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

**[0271]** Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl-and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate.

Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

**[0272]** When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungi static concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

**[0273]** In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

**[0274]** The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

**[0275]** The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

**[0276]** Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

**[0277]** Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

## V. Examples

**[0278]** While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only.

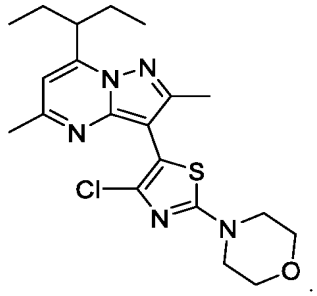
### Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors

**[0279]** Testicular adrenal rest tumors (TART) is a common complication in congenital adrenal hyperplasia (CAH) that is caused by adrenocorticotropin hormone (ACTH)-driven overstimulation of aberrant adrenal cells within the testes and results in impaired spermatogenesis and infertility. TARTS can be found anywhere on the testes, though a typical (very common) location is within the mediastinum. This is a particularly problematic location. Because of the central location of TARTs being in the mediastinum, compression of the nearby seminiferous tubules is common and can lead to obstructive azoospermia, irreversible damage to surrounding tissue, and permanent infertility in males.

**[0280]** Current treatment for TART consists of chronic high-dose glucocorticoids, a problematic therapy with significant side effects and a narrow therapeutic window. Given the serious nature of TART and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with TART. Compound 1, a high-affinity and selective small-molecule antagonist of the corticotropin-releasing factor type-1 ($CRF_1$) receptor, may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a previous proof-of-concept study using a

similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH. Compound 1 has been shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. These promising results provide a rationale for investigating the use of Compound 1 in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.

**[0281]** The structure of Compound 1 is:



**[0282]** Building upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2 proof-of-concept study of Compound 1 in subjects with CAH, this Phase 2 will study Compound 1 specifically in male CAH subjects with TART for the first time. A sample size of approximately 12 subjects was selected to provide sufficient data for an initial evaluation of efficacy and safety in subjects with TART while maintaining feasible subject recruitment goals for this rare condition. Given the rarity of the disease and thus the small sample size that can be recruited, this study will be open label, and all enrolled subjects will receive active study drug. Subjects will serve as their own controls in that their outcome measures after 12 weeks of study drug dosing will be compared to their baseline measures.

**[0283]** The schedule of study visits (every 2 weeks through Week 4, then every 4 weeks for the remainder of the study) provides an appropriate balance between minimizing subject burden and closely monitoring subject safety and response to therapy. The 4-week post-treatment washout period will allow for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

**[0284]** The specification of study drug dosing at 10pm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers. The plasma $C_{max}$ (maximum concentration) for Compound 1 in the Phase 1 studies occurred approximately 5 hours after dosing. Therefore, Compound 1 will be dosed daily at 10pm in this study in order to achieve peak plasma study drug concentration at the time of day when most adrenal androgens are produced. Subjects will consume a standardized snack before taking study drug because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety. **(FIGS. 1A-1B)**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the efficacy of Compound 1 in subjects with TART | • Reduction in the size/volume of TART on testicular ultrasound from screening to Week 12 |
| **Secondary** | |
| • To evaluate the safety of Compound 1 in subjects with TART | • Adverse events (AEs), serious adverse events (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs)<br>• Physical examination findings<br>• Vital signs<br>• Changes in electrocardiogram (ECG)<br>• Changes in clinical laboratory values |
| • To assess the pharmacodynamic (PD) biomarker effects of Compound 1 | • Changes in plasma concentrations of key PD biomarkers, including ACTH, 17-OHP, testosterone, androstenedione, luteinizing hormone (LH), |

(continued)

| | | |
|---|---|---|
| **Secondary** | | |
| | | follicle-stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, and aldosterone from baseline to Week 12 |
| | • To assess changes on semen analysis | • Changes in sperm count, morphology, and motility from baseline to Week 12 |
| | • To assess changes in metabolism | • Changes in metabolic parameters, including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12 |
| | | • Changes in body weight, body mass index (BMI), waist circumference, and blood pressure |
| | • To evaluate changes in quality of life (QoL) and mood | • Changes in QoL measured using the Short Form 36 (SF-36) |
| | | • Changes in mood measured using the Hospital Anxiety and Depression Scale (HADS) |

**Study Population**

**[0285]** Approximately 12 male subjects with TART will be enrolled at approximately 6 investigative sites in the United States, United Kingdom, and possibly other countries. Up to 12 additional subjects may be added to further evaluate specific safety, PD, or efficacy findings.

**Eligibility Criteria**

Inclusion Criteria

**[0286]**

- Adult male subjects aged 18 to 30, inclusive
- Documented historical diagnosis of CAH based on documented genetic mutation or historical documentation of elevated 17-OHP
- Diagnosis of TART via testicular ultrasound and/or magnetic resonance imaging (MRI) at screening with ≥1 lesion(s) measuring ≥2 cm in diameter
- On a stable regimen of GC replacement for ≥30 days before baseline
- Agree to follow contraception guidelines and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug
- Subject is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol Exclusion Criteria
- Any clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:

    o A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
    o Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m$^2$
    o Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
    o Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)

- Any clinically significant psychiatric disorders, including any current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months

- HADS score >12 for either depression or anxiety
- At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at screening and baseline (eg, C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)
- Clinically significant and abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:

    o Clinically meaningful abnormal ECG results, in the opinion of the Investigator
    o Fridericia-corrected QT interval (QTcF) >450 msec
    o Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
    o Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)

- A history that includes bilateral adrenalectomy or hypopituitarism
- Use of any other investigational drug within 30 days or 5 half-lives, whichever is longer, before initial screening
- Require use of prohibited concomitant medications, including strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids, hydrocortisone, and dexamethasone) within 30 days or 5 half-lives (whichever is longer) of first dose of study drug. Medications that are sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
- Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

**Study Duration**

**[0287]** The expected duration of study participation for each subject is up to approximately 20 weeks. This includes a screening period of ≤4 weeks, a treatment period of 12 weeks, and a safety follow-up period of 4 weeks.

**Study Design**

**[0288]** This is a Phase 2, open-label efficacy and safety study of Compound 1 for the treatment of TART. All subjects will receive a daily oral dose of Compound 1 for 12 weeks.In-clinic study visits will occur for screening and at Day 1 (baseline) and Weeks 2, 4, 8, 12 (end of treatment), and 16 (follow-up).

**Dose, Route, Regimen**

**[0289]** All subjects will receive a daily oral dose of Compound 1 for 12 weeks. Subjects will receive 600 mg/day during the first 2 weeks and 1000 mg/day during the remaining 10 weeks of the treatment period. Study drug will be taken daily at 10pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

**[0290]** On mornings of study visits with 8am blood draws for laboratory assessments, subjects should take their morning glucocorticoid replacement after the blood draws. For all other days during the study, subjects may take their morning glucocorticoid replacement at their usual time (generally between 6am and 8am).

**[0291]** If a subject experiences a Grade 3 or higher TEAE considered at least possibly related to study drug, the Investigator may reduce the subject's daily dose of Compound 1 down in increments of 200 mg. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria.

**Investigational Drug**

**[0292]** Compound 1 is a small-molecule $CRF_1$ receptor antagonist and will be supplied as 200-mg, size 1, white, hard gelatin capsules.

**Example 2.**

**[0293]** Since elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1, a

small-molecule antagonist of the $CRF_1$ receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH. The safety profile of Compound 1 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH is currently ongoing.

*Nonclinical Toxicology of Compound 1*

**[0294]** The nonclinical safety profile of Compound 1 has been evaluated in repeat-dose range-finding and definitive toxicology studies of up to 91 days in duration in rats and dogs using the clinically relevant route (oral) and schedule of administration (once daily). In rats and beagle dogs administered oral Compound 1 once daily for 91 consecutive days at doses up to 2000 mg/kg/day, toxicologic findings were all mild and limited to the male reproductive tract, and all Compound 1-related findings were reversible following a 6-week treatment-free recovery period.

**[0295]** Additionally, a fertility toxicology study was conducted in rats. In this study, male rats were administered oral Compound 1 once daily at 0, 5, 20, or 1000 mg/kg for 85 to 87 days (70 days before mating, during mating, and ≤4 days between mating and necropsy). Male reproductive performance (mean day of mating, mating and fertility indices, and conception rates) was unaffected by Compound 1 treatment. Untreated females mated with the Compound 1-treated males had no ovarian and uterine effects.

**[0296]** In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay have also been conducted.

*Clinical Experience with Compound 1*

**[0297]** To date, a total of 53 subjects, all healthy adults aged 21 to 65 years, have been treated with at least 1 dose of Compound 1 in 2 Phase 1 studies. The first-in-human study of Compound 1 (Study I3C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study I3C-FW-BLAB) evaluated repeat doses of 50 mg, 100 mg, or 200 mg Compound 1 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs). Compound 1 has been well tolerated in healthy human subjects, with no SAEs, AEs leading to discontinuation, or dose-limiting toxicities (DLTs). A maximum tolerated dose has not been reached in humans.

**[0298]** An ongoing Phase 2 open-label study (Study Compound 2) is currently evaluating the safety and efficacy of Compound 1 dosed once daily for 6 weeks in adults with classic CAH. In the initial Cohort A of this study, all subjects are dosed starting at 200 mg/day for 14 days, escalating for each subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLTs at the previous dose level. (FIGS. 2-3).

*Known Potential Risks*

**[0299]** Because the reversible testicular effects (degeneration/atrophy) observed in rats and dogs treated with high-dose Compound 1 (2,000 mg/kg/day) are likely associated with on-target (mechanism-driven) effects, these effects are likely to be relevant to human risk. However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical laboratory markers of testicular function (LH and FSH) when Compound 1 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Clinical laboratory measures of testicular function (LH, FSH, inhibin B, and SHBG) will be assessed throughout this study to monitor the risk of testicular injury. Testicular ultrasounds and semen analysis will also be performed at screening/baseline and the end of the treatment period.

**[0300]** Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the Phase 1 clinical studies. Clinical laboratory measures of liver chemistry will be assessed throughout this study, and strict individual treatment stopping criteria for liver chemistry findings are in place.

**[0301]** Compound 1-induced effects on the thyroid gland were noted in dogs after 91 days of high-dose (2,000 mg/kg/day) treatment but not in any other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) were not evaluated in the Phase 1 studies but will be monitored throughout this study.

*Known Potential Benefits*

**[0302]** Early clinical studies suggests that Compound 1 is effective as a $CRF_1$ receptor antagonist, a mechanism of action that supports the clinical investigation of Compound 1 for treatment of TART. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH.

*Assessment of Potential Risks and Benefits*

**[0303]** The mild and reversible toxicologic effects of Compound 1 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a $CRF_1$ receptor antagonist, Compound 1 is intended to reduce abnormally elevated ACTH levels, which in TART drives overstimulation of aberrant adrenal cells within the testes. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. In TART, where baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

**[0304]** Given the serious nature of TART and the limitations (and risks) of chronic steroid therapy, new treatment modalities are needed for patients with TART. Given the acceptable safety and tolerability profile of Compound 1 in healthy volunteers from the Phase 1 program, the low probability of demonstrating meaningful PD marker changes in healthy subjects, and the lack of any clear benefit to exposing more healthy subjects to study drug, the Sponsor believes the benefit-to-risk profile favors the entry of Compound 1 into Phase 2 in subjects with TART.

**Example 3. Congenital Andrenal Hyperplasia (CAH)**

**[0305]** CAH results from a genetic defect in the 21-hydroxylase enzyme. CAH patients are thus unable to produce cortisol. Without cortisol to provide negative feedback, patients over-produce ACTH. High ACTH promotes the overproduction of potent androgens (male sex hormones). Without wishing to be bound by theory, Compound 1 blocks $CRF_1$ receptor to prevent ACTH release by the pituitary and associated drive on the hypothalamic-pituitary-adrenal axis. Replacement of cortisol to physiological levels will correct cortisol deficiency, however, will not lower ACTH, resulting in hyperplasia of adrenal gland and associated overproduction of adrenal androgens.

**[0306]** As shown in **FIGS. *4*** and **5A-5B,** the attenuation of ACTH demonstrates target engagement and functional $CRF_1$ receptor antagonism. 80% of subjects demonstrated reduction in ACTH. 70% of subjects demonstrated > 25% reduction in ACTH. 30% of subjects were in the normal range (*) after treatment with a $CRF_1$ receptor antagonist.

**[0307]** **FIGS. *6*** and **7A-7B** demonstrate "control" of disease based on standard guidelines, which would then allow steroid taper. 80% of subjects demonstrated reduction in 17-OHP. 50% of subjects demonstrated > 25% reduction in ACTH. 50% of subjects were in the guideline range (*; 1200 ng/dL) after treatment with a $CRF_1$ receptor antagonist.

**[0308]** **FIGS. *8*** and **9A-9B** demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess andreogen production and associated symptoms. 100% of subjects demonstrated reduction in androstenedione (at various doses). 60% of subjects demonstrated > 25% reduction in androstenedione. 50% of subjects were within the normal reference range after treatment with a $CRF_1$ receptor antagonist.

**[0309]** ***FIGS. 10A-10B*** show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a $CRF_1$ receptor antagonist.

**[0310]** ***FIGS. 11A-11B*** demonstrate Compound 1 is a potent, selective, and functional $CRF_1$ receptor antagonist. In in vitro and ex vivo studies, Compound 1 was determined to be a potent and selective $CRF_1$ receptor antagonist with high affinity and selective for the $hCRF_1$ receptor. Compound 1 was found to have functional potency to inhibit adenylate cyclase activity ($CRF_1$ receptor-mediated downstream cascade), demonstrating in vitro efficacy as a $CRF_1$ receptor antagonist. Compound 1 was found to significantly inhibit CRF-induced locomotor behavior in response to i.c.v. administration of CRF (**FIG. 11B**).

**[0311]** ***FIGS. 12A-12B*** demonstrate single pill of $CRF_1$ receptor antagonist improves ACTH and 17-OHP in CAH patients.

**[0312]** ***FIG. 13*** shows the subject level hormone changes (ACTH, 17-OHP, and androstenedione) by dose of a $CRF_1$ receptor antagonist.

***Example 4. Assess reduction in excess ACTH and adrenal steroid production***

**[0313]** The objectives of the study are: to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable gluococorticoid regimen; to evaluate the safety and tolerability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

*ELIGIBILITY CRITERIA*

**[0314]** Inclusion Criteria:

- Adult males and females 18 years or older
- Diagnosis of classic CAH due to 21-hydroxylase deficiency
- Morning 17OHP ≥800 ng/dL, before taking any morning GC dose
- On a stable regimen of gluococorticoid replacement for ≥30 days before enrollment

**[0315]** Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease within 30 days of screening
- Clinically significant psychiatric disorder
- History of bilateral adrenalectomy or hypopituitarism

*STUDY DESIGN*

**[0316]** FIG. 14 depicts the proof of concept and escalating QD dosing at 10 PM for Cohort A and the single dose level and BID dosing at 10 AM and 10 pm for Cohort B.

**BASELINE CHARACTERISTICS**

**[0317]** Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 partcipants were enrolled and received at least 1 dose of Compound 1. One participant withdrew early because of an occupation-related scheduling conflict. In Cohort B, 9 participants were enrolled and received at least one dose of Compound 1. One participant was withdrawn upon discovery of a major protocol violation at Baseline and did not have postbaseline efficacy/PK data. Thus, baseline characteristics are calculated for n=8 in Cohort B. One participant in Cohort B was taking both HC and prednisone.

Table - 1 Baseline characteristics of each cohort

| Parameter | | Cohort A (n=10) | Cohort B (n=8) |
|---|---|---|---|
| Demographics | | | |
| | Age (years), mean (range) | 39.3 (24-66) | 36.8 (19-66) |
| | Sex | 5M, 5F | 1M, 7F |
| | Bmi (kg/m$^2$), mean ± SD | 31.5 ± 12.0 | 31.1 ± 6.7 |
| Daily GC dose (mg HC equivalents), mean range | | 28 (13-40) | 35 (20-50) |
| Types of GCs | | 4 JC, 3 pred, 3 dex | 2HC, 4 pred, 3 dex |
| 17OHP at screening[a] (ng/dl), mean ± SD | | 5,985 ± 6,347 | 4,592 ±4,624 |
| Abbreviations: 17OHP: 17-hydroxyprogesterone; BMI: body mass index; dex: dexamethasone; F: female; GC: glucocorticoid; HC: hydrocortisone; M: male; pred: prednisone; SD: standard deviation<br>a 17OHP reference ranges: 27-199 ng/dL males, 15-290 ng/dL females. | | | |

*SAFETY*

**[0318]** Across both cohorts, Compound 1 was generally well tolerated. The most common type of adverse event (AE) was gastrointestinal disorders There were no serious AEs and no AEs leading to withdrawal.

**PHARMACOKINETICS**

**[0319]** Over a wide range of doses (200 to 1000 mg QD), Compound 1 exhibited a predictable, dose-dependent PK profile.

*EFFICACY*

**[0320]** ***FIG.*** **15A-15D** show the changes in levels of Androstenedione (A4) across both cohorts. Levels of A4 improved at ≥1 dose level for 10 out of 10 participants in Cohort A and 6 out of 8 participants in Cohort B. Excess A4 is associated with clinical sequelae in CAH. Attenuation of A4 demonstrates control of adrenal androgen.

**[0321]** **FIG. 16A-16D** show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 6 out of 7 participants in Cohort B. 17OHP is a critical hormone in CAH diagnosis and management. Attenuation of 17OHP demonstrates control of adrenal steroid production.

**[0322]** **FIG. 17A-17D** show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 5 out of 7 participants in Cohort B. Attenuation of ACTH demonstrates target engagement and fucntional $CRF_1$ receptor antagonism.

*Table 2 - Percentage change from baseline in ACTH,* 17OHP *and A4.*

| | Cohort A | | | Cohort B |
|---|---|---|---|---|
| | 200 mg QD (Week 2) | 600 mg QD (Week 4) | 1000 mg QD (Week 6) | 200 mg BID (Weed 2) |
| ACTH | -25.7 (±51.6) | -60.1 (±37.5) | -32.7 (±47.0) | -36.5 (±58.0) |
| 17OHP | +22.2 (±172.3) | -23.7 (±64.2) | -13.8 (±74.7) | -47.8 (±63.3) |
| A4 | -12.1 (±47.4) | -33.2 (±36.5) | -28.6 (±44.6) | -16.0 (±81.4) |

**CONCLUSIONS**

**[0323]** Compound 1, a potent and selective $CRF_1$ receptor antagonist, offers a novel nonsteroidal oral treatment approach for CAH. Compound 1 was well tolerated and efficacious in reducing excess ACTH, 17OHP, and androstenedione in patients with classic CAH. Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

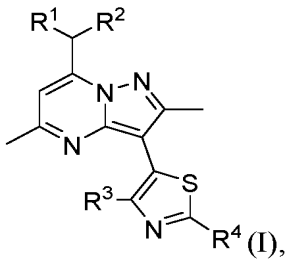
**Claims**

1. A corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof.

2. The $CRF_1$ antagonist for use according to claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).

3. The $CRF_1$ antagonist for use according to claim 1, wherein the treatment is a reduction in the size and/or the number of the tumors.

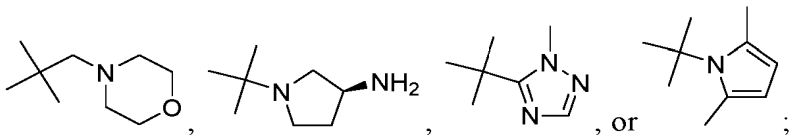
4. The $CRF_1$ antagonist for use according to claim 1, wherein the $CRF_1$ antagonist comprises a compound having structural Formula (I):




(I),

or a pharmaceutically acceptable salt thereof,
wherein:

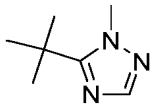
$R^1$ and $R^2$ are independently ethyl or n-propyl;
$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and
$R^4$ is hydrogen, Br, $R^aR^bN$-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



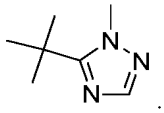
$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-.

**5.** The $CRF_1$ antagonist for use according to claim 4, wherein $R^3$ is Cl, Br, or methyl.

**6.** The $CRF_1$ antagonist for use according to claim 4, wherein $R^4$ is Br, $R^aR^bN$-, pyridin-4-yl, morpholin-4-yl, or

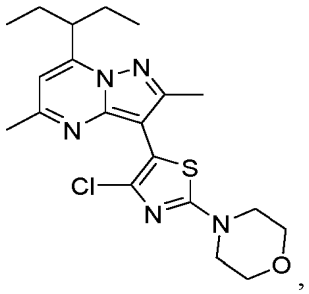


**7.** The $CRF_1$ antagonist for use according to claim 4, wherein $R^4$ is morpholin-4-yl or



**8.** The $CRF_1$ antagonist for use according to claim 4, wherein $R^4$ is hydrogen, Br, $R^aR^bN$- and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

**9.** The $CRF_1$ antagonist for use according to claim 4, wherein the compound is



or a pharmaceutically acceptable salt thereof.

**10.** The $CRF_1$ antagonist for use according to claim 1, wherein a dosage regime of the $CRF_1$ antagonist, or a pharmaceutically acceptable salt thereof, is about 5 mg/day to about 400 mg/day to the subject.

**11.** The $CRF_1$ antagonist or a pharmaceutically acceptable salt thereof for use according to claim 1, for use in oral administration.

**12.** The $CRF_1$ antagonist for use according to claim 1, wherein the $CRF_1$ antagonist, or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

**13.** The $CRF_1$ antagonist of claim 1 and an additional chemotherapeutic agent, for use in the treatment or prevention of testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, wherein

the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen.

**14.** The $CRF_1$ antagonist and the additional chemotherapeutic agent for use according to claim 13, wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.

**15.** The $CRF_1$ antagonist for use according to claim 4, wherein $R^3$ is Cl, Br, methyl, or trifluoromethyl.

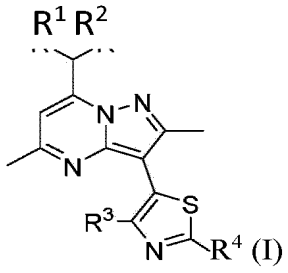
**Patentansprüche**

**1.** Corticotropin-releasing-Faktor-Typ-1 ($CRF_1$)-Antagonist oder ein pharmazeutisch verträgliches Salz davon zur Verwendung bei der Behandlung oder Vorbeugung von testikulären adrenalen Resttumoren (TART) oder ovariellen adrenalen Resttumoren (OART) bei einem Subjekt, das dessen bedarf.

**2.** $CRF_1$-Antagonist zur Verwendung nach Anspruch 1, wobei der Patient eine kongenitale Nebennierenhyperplasie (CAH) hat.

**3.** $CRF_1$-Antagonist zur Verwendung nach Anspruch 1, wobei die Behandlung in einer Verringerung der Größe und/oder der Anzahl der Tumore besteht.

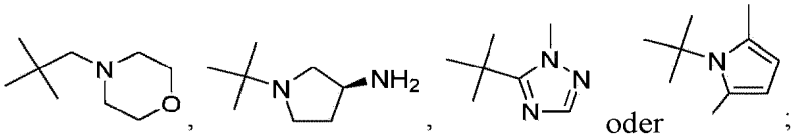
**4.** $CRF_1$-Antagonist zur Verwendung nach Anspruch 1, wobei der $CRF_1$-Antagonist eine Verbindung 10 mit der Strukturformel (I) umfasst:




(I)

oder ein pharmazeutisch verträgliches Salz davon, wobei:

$R^1$ und $R^2$ unabhängig voneinander Ethyl oder n-Propyl sind;
$R^3$ Wasserstoff, Cl, Br, Methyl, Trifluormethyl oder Methoxy ist; und
$R^4$ Wasserstoff, Br, $R^aR^bN$-, Methoxymethyl, n-Butyl, Acetamido, Pyridin-4-yl, Morpholin-4-yl,

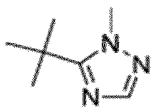



;

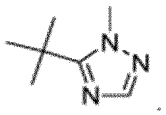
ist
$R^a$ und $R^b$ unabhängig voneinander Wasserstoff, $C_1$-$C_3$-Alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$- oder $CH_3CH_2CH_2NHCH_2CH_2$- sind.

**5.** $CRF_1$-Antagonist zur Verwendung nach Anspruch 4, wobei $R^3$ Cl, Br oder Methyl ist.

**6.** $CRF_1$-Antagonist zur Verwendung nach Anspruch 4, wobei $R^4$ Br, $R^aR^bN$-, Pyridin-4-yl, Morpholin-4-yl oder Folgendes ist:

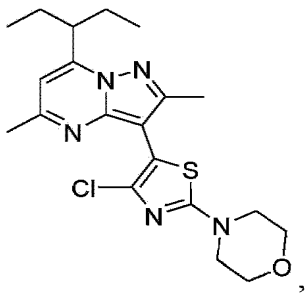


7. $CRF_1$-Antagonist zur Verwendung nach Anspruch 4, wobei $R^4$ Morpholin-4-yl oder Folgendes ist:



8. $CRF_1$-Antagonist zur Verwendung nach Anspruch 4, wobei $R^4$ Wasserstoff, Br, $R^aR^bN$-ist und $R^a$ und $R^b$ unabhängig voneinander $C_1$-$C_3$-Alkyl sind.

9. $CRF_1$-Antagonist zur Verwendung nach Anspruch 4, wobei die Verbindung



oder ein pharmazeutisch verträgliches Salz davon ist.

10. $CRF_1$-Antagonist zur Verwendung nach Anspruch 1, wobei das Dosierungsschema des $CRF_1$-Antagonisten oder eines pharmazeutisch verträglichen Salzes davon etwa 5 mg/Tag bis etwa 400 mg/Tag für das Subjekt beträgt.

11. $CRF_1$-Antagonist oder ein pharmazeutisch verträgliches Salz davon zur Verwendung nach Anspruch 1 zur Verwendung bei oraler Verabreichung.

12. $CRF_1$-Antagonist zur Verwendung nach Anspruch 1, wobei der $CRF_1$-Antagonist oder ein pharmazeutisch verträgliches Salz davon als Kapsel oder Tablette formuliert ist.

13. $CRF_1$-Antagonist nach Anspruch 1 und zusätzliches chemotherapeutisches Mittel zur Verwendung bei der Behandlung oder Vorbeugung von testikulären adrenalen Resttumoren (TART) oder ovariellen adrenalen Resttumoren (OART) bei einem Subjekt, das dessen bedarf, wobei das zusätzliche chemotherapeutische Mittel ein Glucocorticoid, ein Mineralocorticoid, ein ACAT 1-Inhibitor oder ein Antiandrogen ist.

14. $CRF_1$-Antagonist und zusätzliches chemotherapeutisches Mittel zur Verwendung nach Anspruch 13, wobei das Glucocorticoid Beclomethason, Betamethason, Budesonid, Cortison, Dexamethason, Hydrocortison, Methylprednisolon, Prednisolon, Prednison oder Triamcinolon ist.

15. $CRF_1$-Antagonist zur Verwendung nach Anspruch 4, wobei $R^3$ Cl, Br, Methyl oder Trifluormethyl ist.

**Revendications**

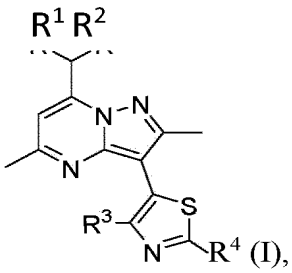
1. Un antagoniste du facteur de libération de corticotropine de type 1 ($CRF_1$) ou un sel pharmaceutiquement acceptable de celui-ci, destiné à être utilisé dans le traitement ou la prévention des tumeurs surrénaliennes testiculaires au repos (TART) ou des tumeurs surrénaliennes ovariennes au repos (OART) chez un sujet qui le nécessite

2. L'antagoniste du $CRF_1$ destiné à être utilisé selon la revendication 1, dans lequel le sujet présente une hyperplasie

congénitale des surrénales (CAH).

3. L'antagoniste du $CRF_1$ destiné à être utilisé selon la revendication 1, dans lequel le traitement consiste en une réduction de la taille et/ou du nombre des tumeurs.

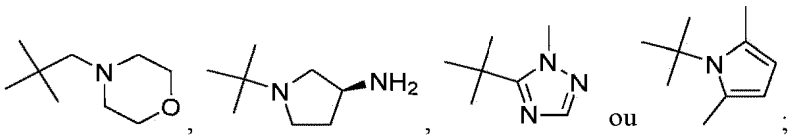
4. L'antagoniste du $CRF_1$ destiné à être utilisé selon la revendication 1, **caractérisé en ce que** l'antagoniste du $CRF_1$ comprend un composé 10 répondant à la formule structurale (I) :



(I),

ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel :

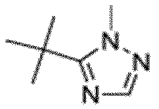
$R^1$ et $R^2$ représentent indépendamment un éthyle ou un n-propyle ;
$R^3$ représente un hydrogène, Cl, Br, méthyle, trifluorométhyle ou méthoxy ; et
$R^4$ représente un hydrogène, Br, $R^aR^bN$-, méthoxyméthyle, n-butyle, acétamido, pyridine-4-yle, morpholine-4-yle,



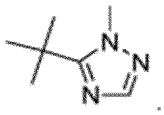
$R^a$ et $R^b$ représentent indépendamment un hydrogène, un alkyle en $C_1$-$C_3$, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, ou $CH_3CH_2CH_2NHCH_2CH_2$-.

5. L'antagoniste du $CRF_1$ destiné à être utilisé selon la revendication 4, dans lequel $R^3$ représente un Cl, Br ou méthyle.

6. L'antagoniste du $CRF_1$ destiné à être utilisé selon la revendication 4, dans lequel $R^4$ représente un Br, $R^aR^bN$-, pyridine-4-yle, morpholine-4-yle, ou

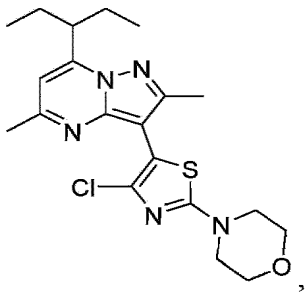


7. L'antagoniste du $CRF_1$ destiné à être utilisé selon la revendication 4, dans lequel $R^4$ est un morpholine-4-yle ou



8. L'antagoniste du $CRF_1$ destiné à être utilisé selon la revendication 4, dans lequel $R^4$ représente un hydrogène, Br, $R^aR^bN$- et $R^a$ ainsi que $R^b$ sont indépendamment un alkyle en $C_1$-$C_3$.

9. L'antagoniste du $CRF_1$ destiné à être utilisé selon la revendication 4, dans lequel le composé est



ou un sel pharmaceutiquement acceptable de celui-ci.

**10.** L'antagoniste du $CRF_1$ destiné à être utilisé selon la revendication 1, dans lequel un schéma posologique de l'antagoniste du $CRF_1$, ou d'un sel pharmaceutiquement acceptable de celui-ci, est d'environ 5 à 400 mg/jour pour le sujet.

**11.** L'antagoniste du $CRF_1$ ou un sel pharmaceutiquement acceptable de celui-ci destiné à être utilisé selon la revendication 1, pour une utilisation en administration orale

**12.** L'antagoniste du $CRF_1$ destiné à être utilisé selon la revendication 1, dans lequel l'antagoniste du $CRF_1$, ou un sel pharmaceutiquement acceptable de celui-ci, est formulé sous forme de capsule ou de comprimé.

**13.** L'antagoniste du $CRF_1$ de la revendication 1 et un agent chimiothérapeutique supplémentaire, destinés à être utilisés dans le traitement ou la prévention des tumeurs surrénaliennes testiculaires au repos (TART) ou des tumeurs surrénaliennes ovariennes au repos (OART) chez un sujet le nécessitant, l'agent chimiothérapeutique supplémentaire étant un glucocorticoïde, un minéralocorticoïde, un inhibiteur de l'ACAT1 ou un antiandrogène.

**14.** L'antagoniste du $CRF_1$ et l'agent chimiothérapeutique supplémentaire destinés à être utilisés selon la revendication 13, dans lesquels le glucocorticoïde est la béclométhasone, la bétaméthasone, le budésonide, la cortisone, la dexaméthasone, l'hydrocortisone, la méthylprednisolone, la prednisone ou la triamcinolone

**15.** L'antagoniste du CRF1 destiné à être utilisé selon la revendication 4, dans lequel $R^3$ représente un Cl, Br, méthyle ou trifluorométhyle.

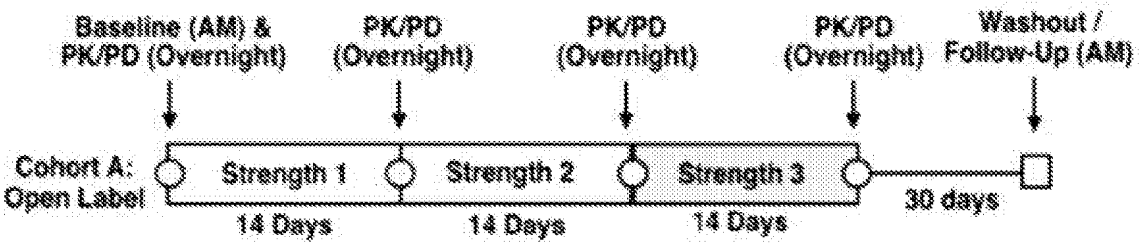

Baseline (AM) & PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
Washout / Follow-Up (AM)
Cohort A: Open Label
Strength 1
Strength 2
Strength 3
30 days
14 Days
14 Days
14 Days

*FIG. 1A*

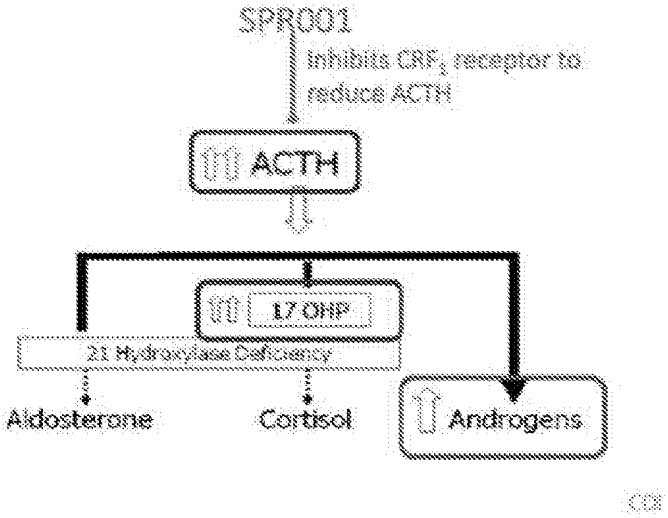

SPR001
Inhibits CRF1 receptor to reduce ACTH
ACTH
17 OHP
21 Hydroxylase Deficiency
Aldosterone
Cortisol
Androgens

*FIG. 1B*

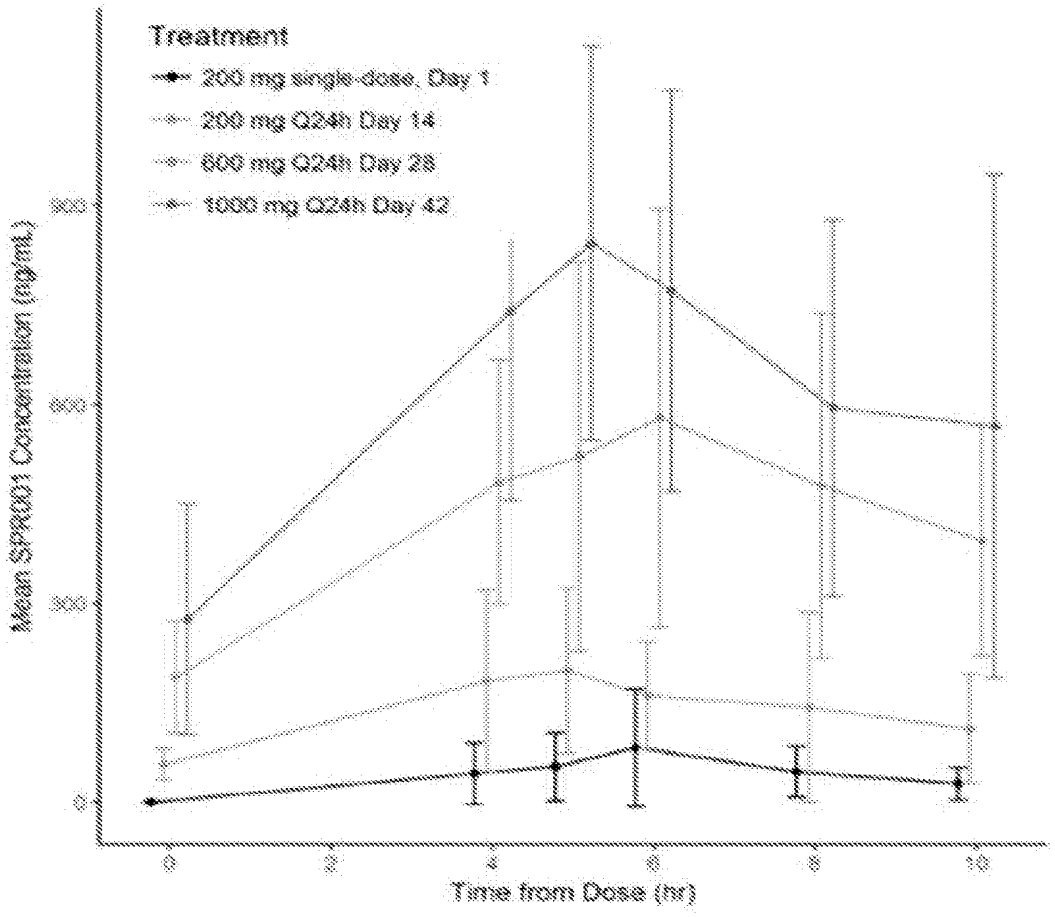

Treatment
200 mg single-dose, Day 1
200 mg Q24h Day 14
600 mg Q24h Day 28
1000 mg Q24h Day 42
Mean SPR001 Concentration (ng/mL)
Time from Dose (hr)

*FIG. 2*

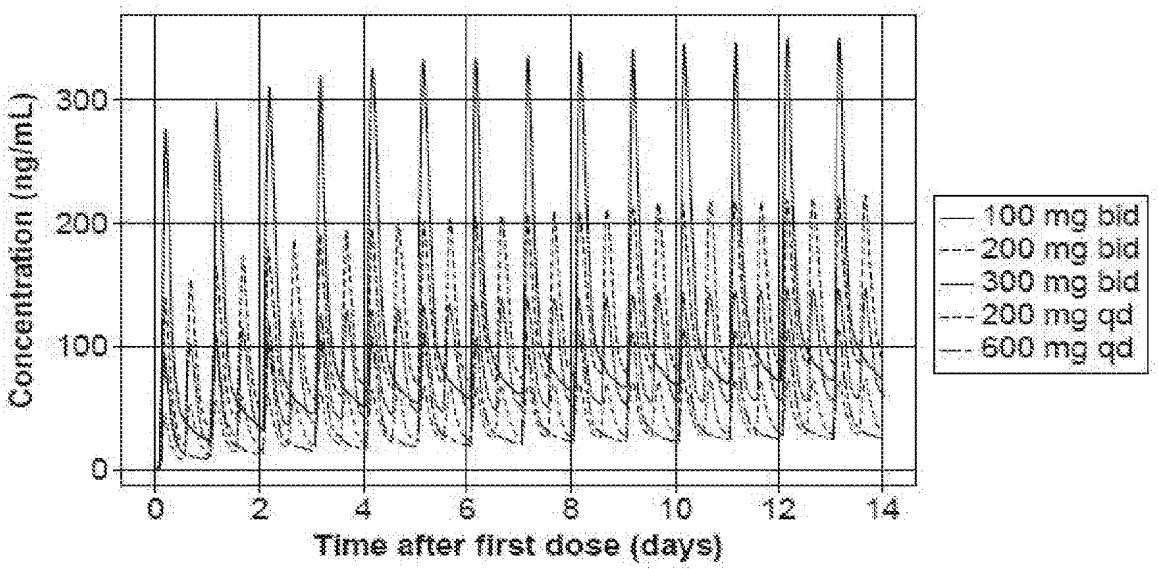

Concentration (ng/mL)
300
200
100
0
0
2
4
6
8
10
12
14
Time after first dose (days)
100 mg bid
200 mg bid
300 mg bid
200 mg qd
600 mg qd

FIG. 3

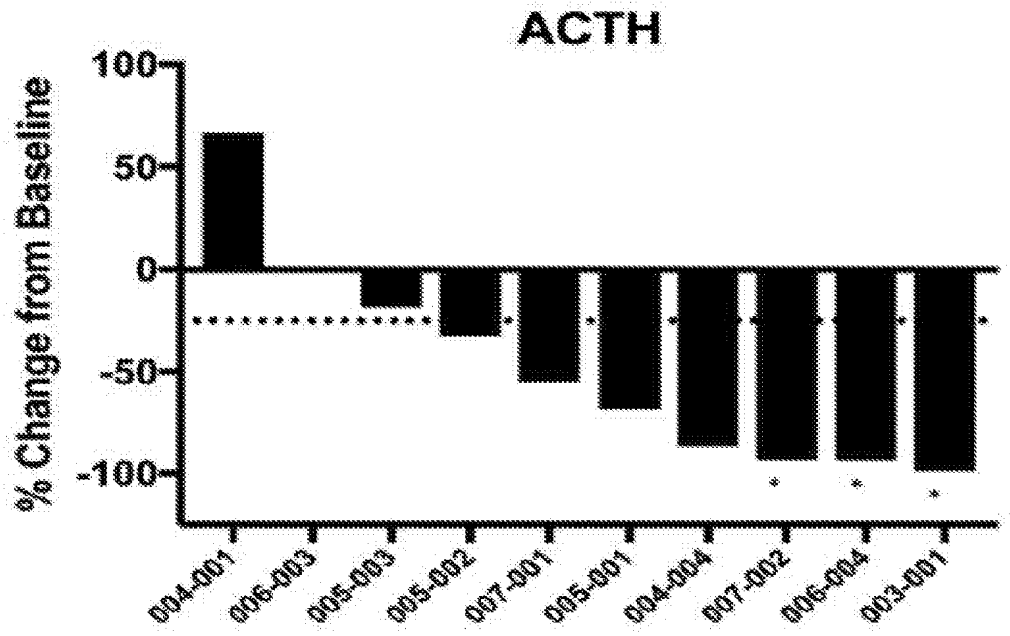

ACTH
% Change from Baseline
100
50
0
-50
-100
004-001
006-003
005-003
005-002
007-001
005-001
004-004
007-002
006-004
003-001

FIG. 4

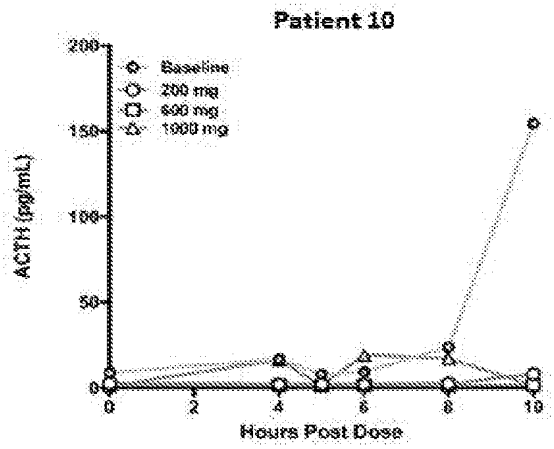



FIG. 5A

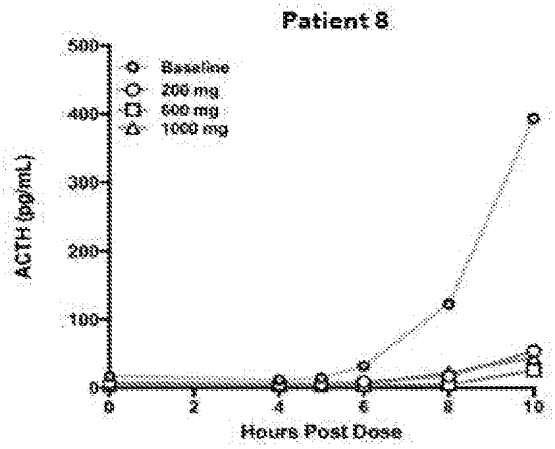



FIG. 5B

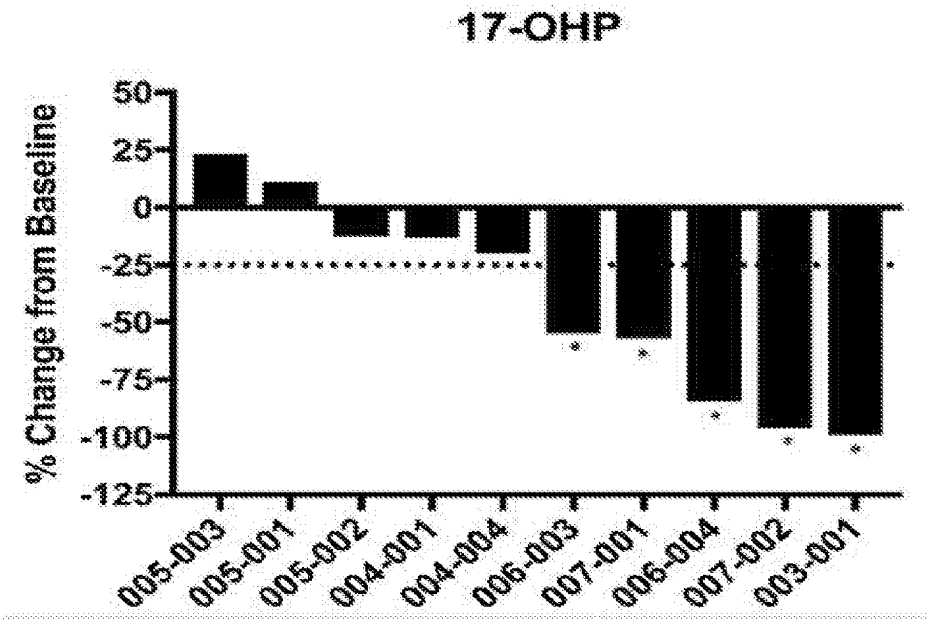



FIG. 6

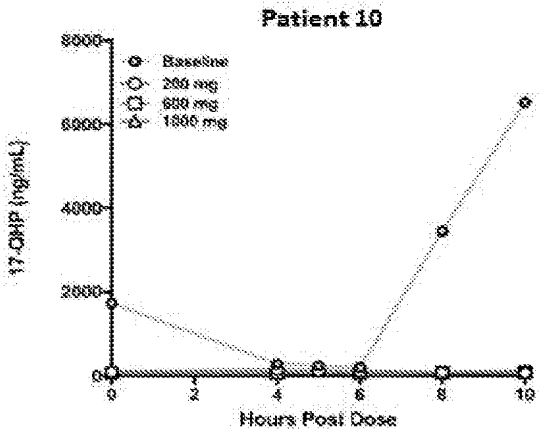



FIG. 7A

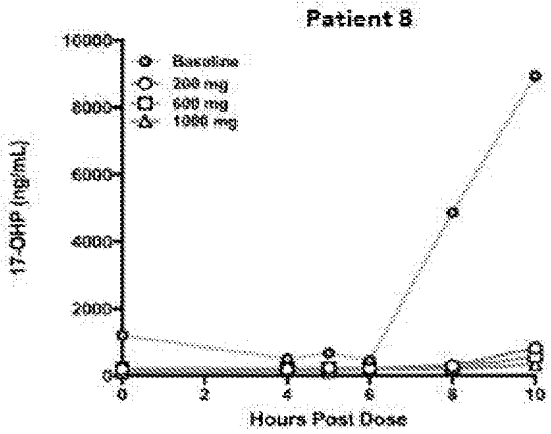



FIG. 7B

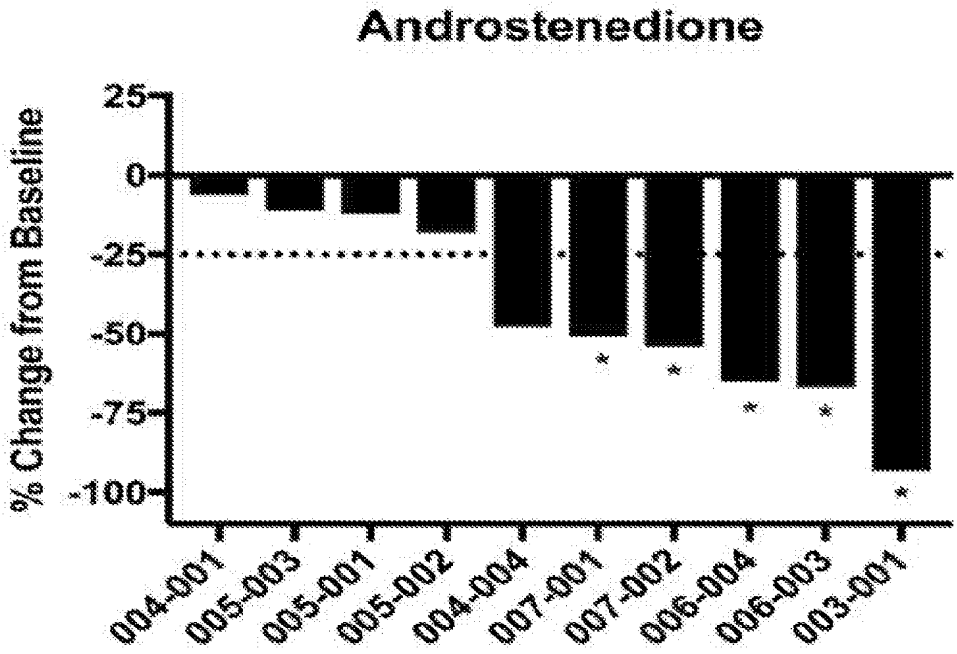



FIG. 8

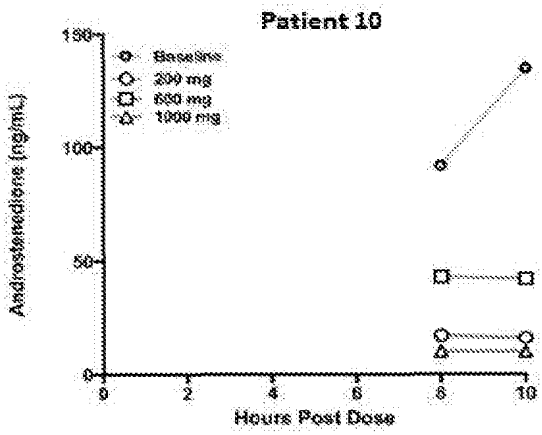



FIG. 9A

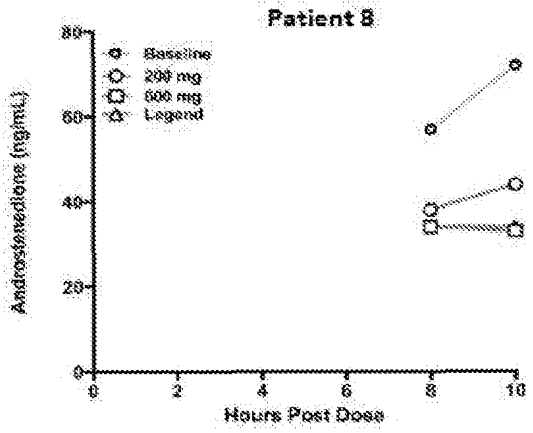



FIG. 9B

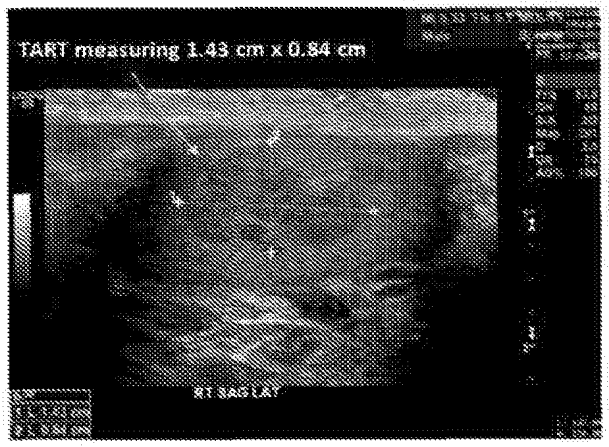



FIG. 10A

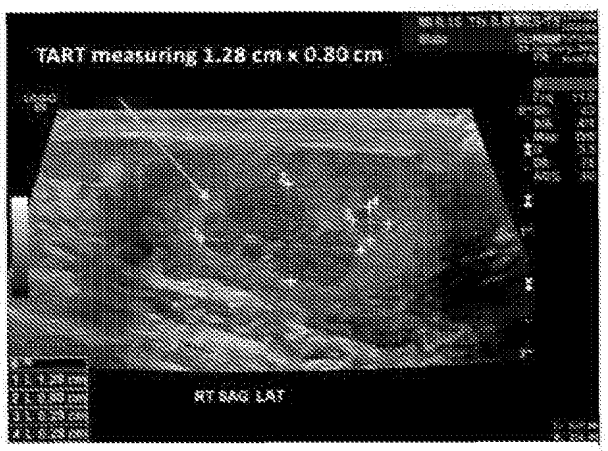



FIG. 10B

In Vitro Binding Assay

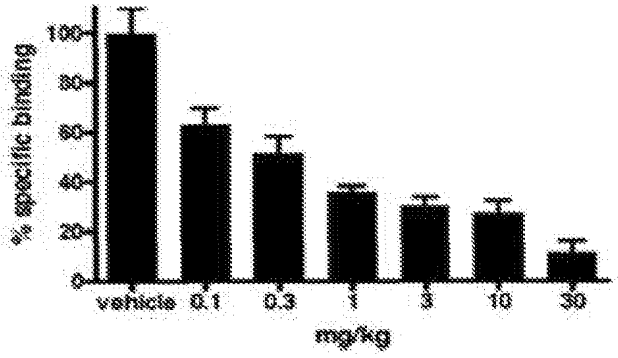



FIG. 11A

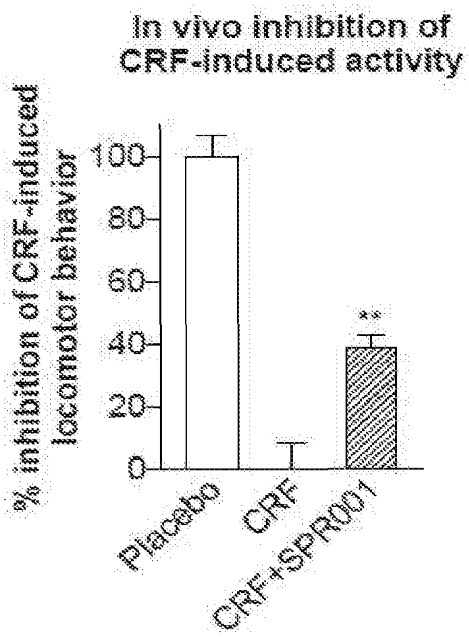



FIG. 11B

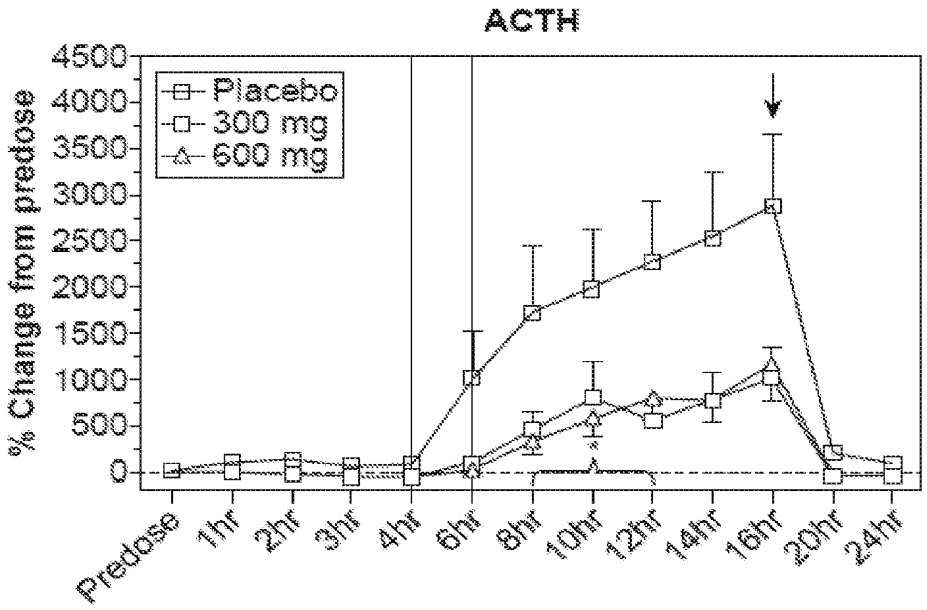



FIG. 12A

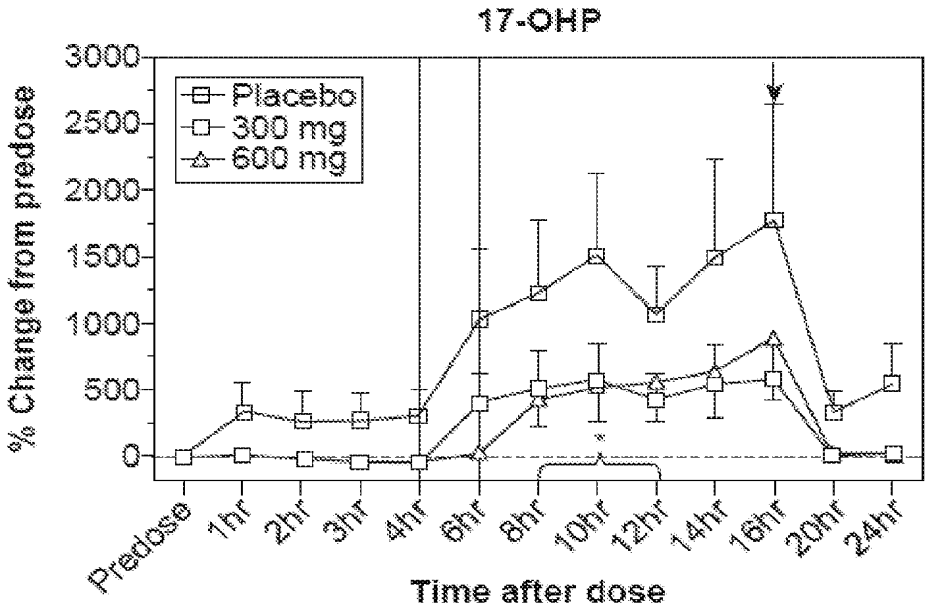



FIG. 12B

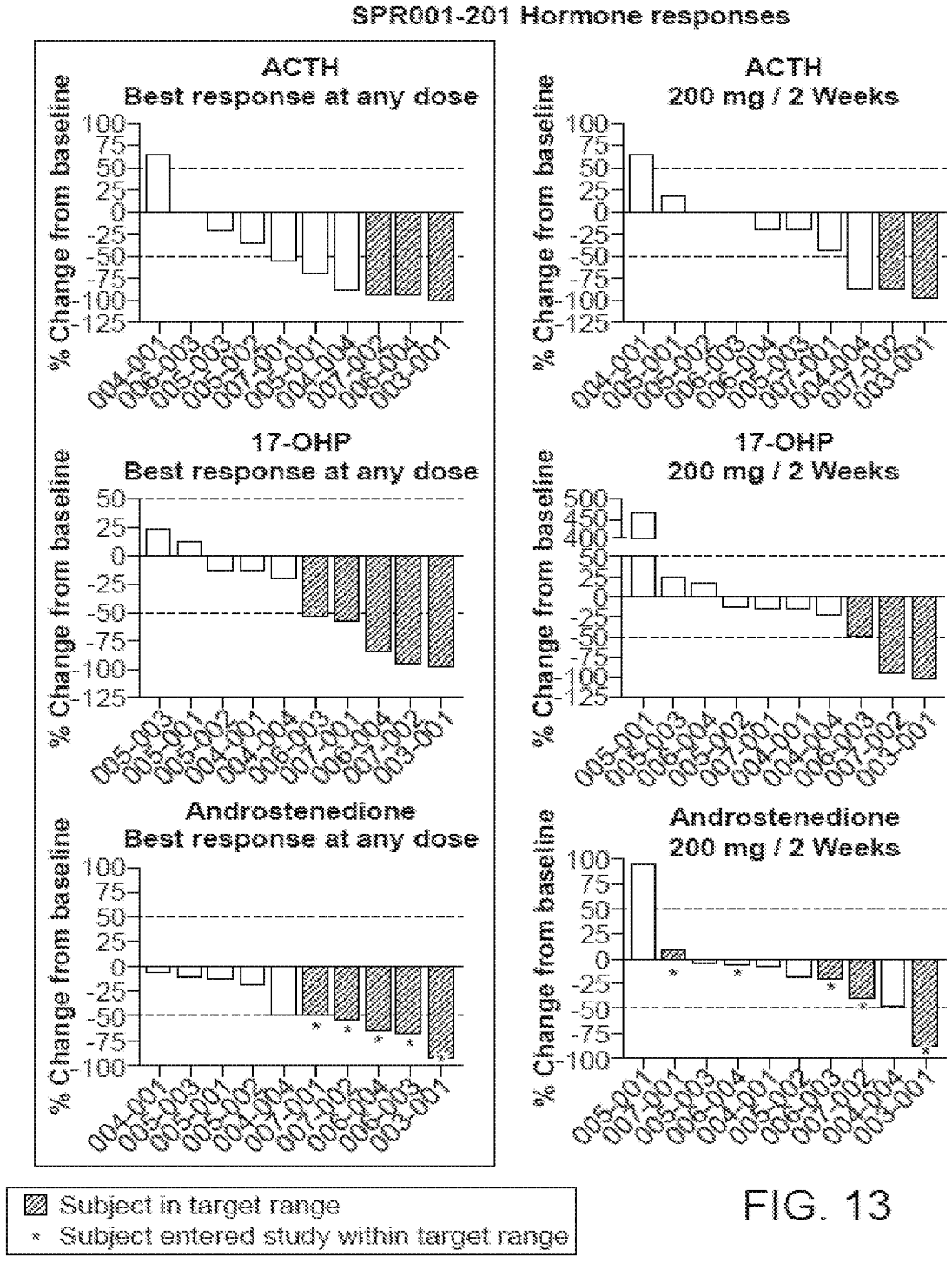



FIG. 13

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

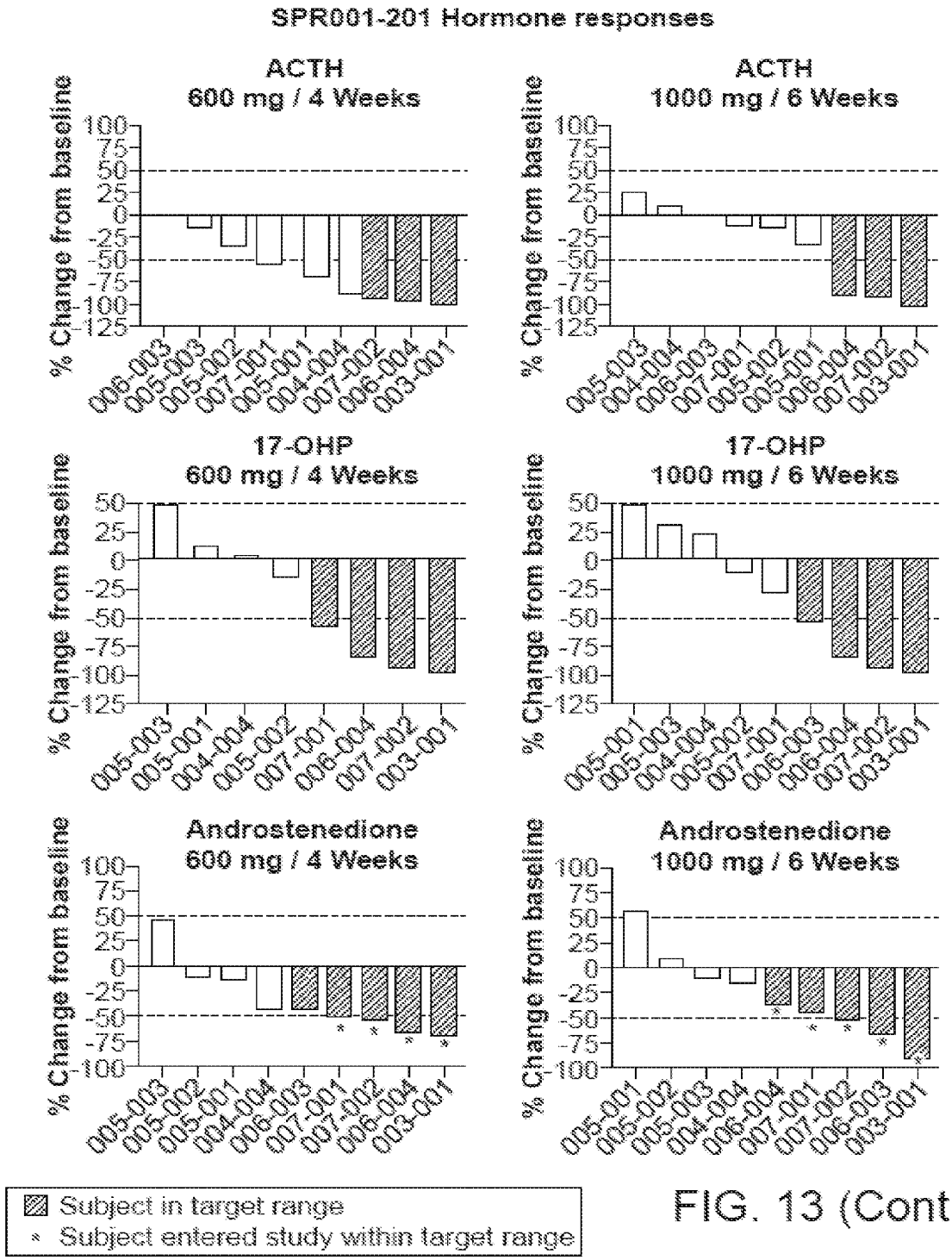



FIG. 13 (Cont.)

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

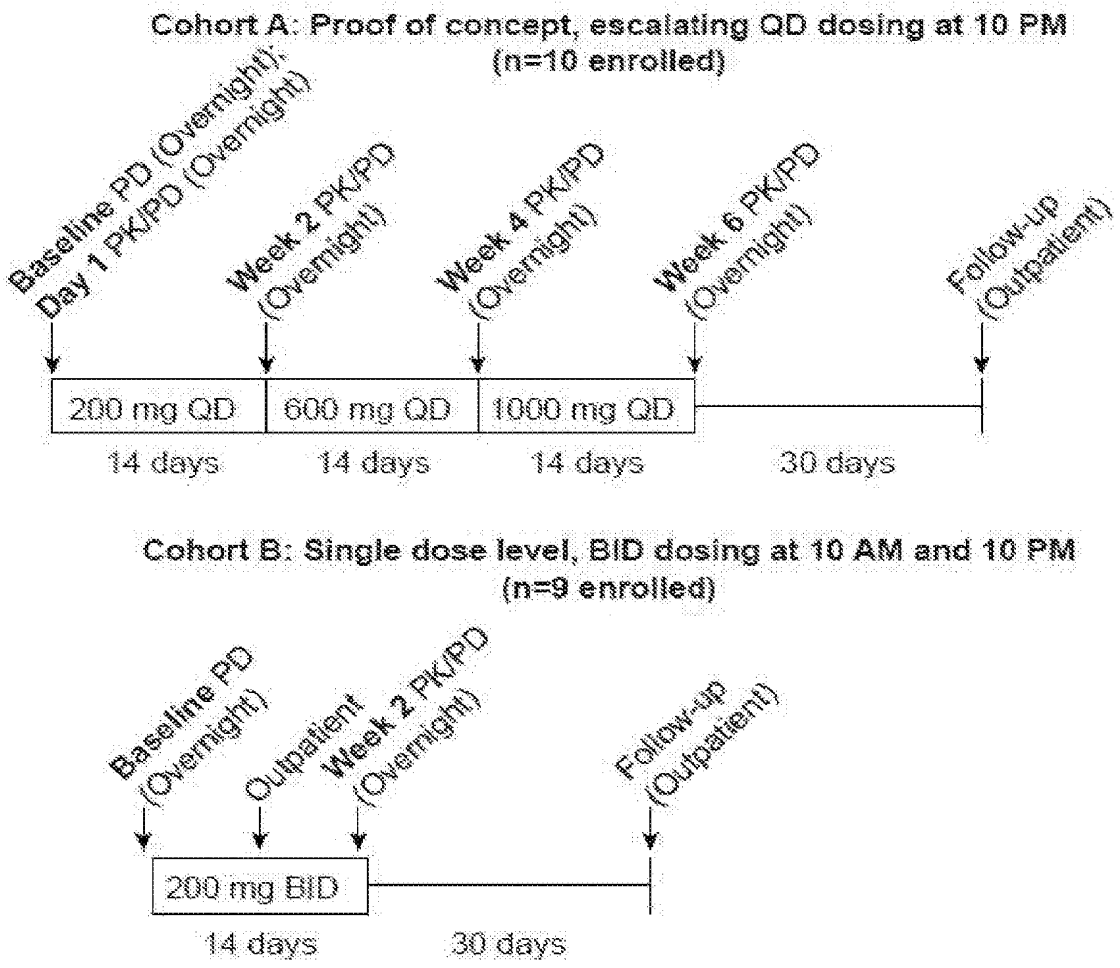

Cohort A: Proof of concept, escalating QD dosing at 10 PM
(n=10 enrolled)
Baseline PD (Overnight); Day 1 PK/PD (Overnight)
Week 2 PK/PD (Overnight)
Week 4 PK/PD (Overnight)
Week 6 PK/PD (Overnight)
Follow-up (Outpatient)
200 mg QD
600 mg QD
1000 mg QD
14 days
14 days
14 days
30 days
Cohort B: Single dose level, BID dosing at 10 AM and 10 PM
(n=9 enrolled)
Baseline PD (Overnight)
Outpatient
Week 2 PK/PD (Overnight)
Follow-up (Outpatient)
200 mg BID
14 days
30 days

FIG. 14

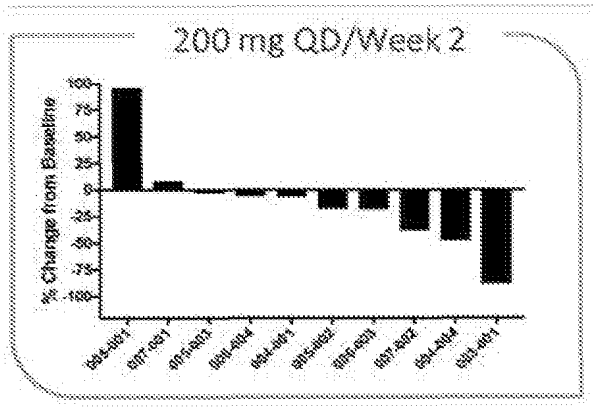



FIG. 15A

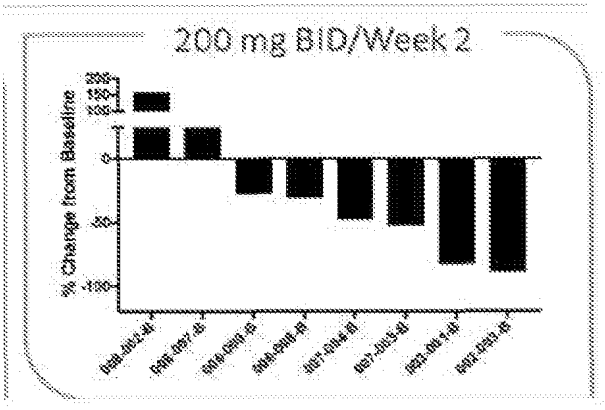



FIG. 15B

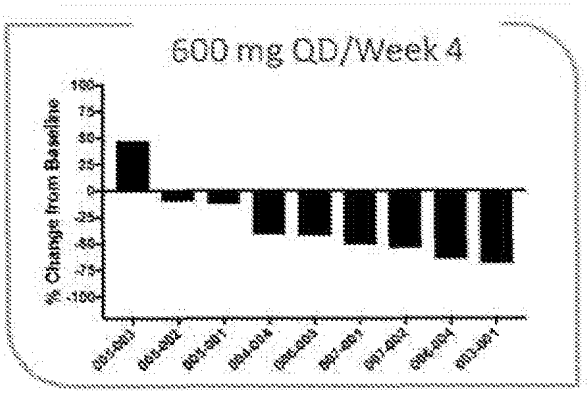



FIG. 15C

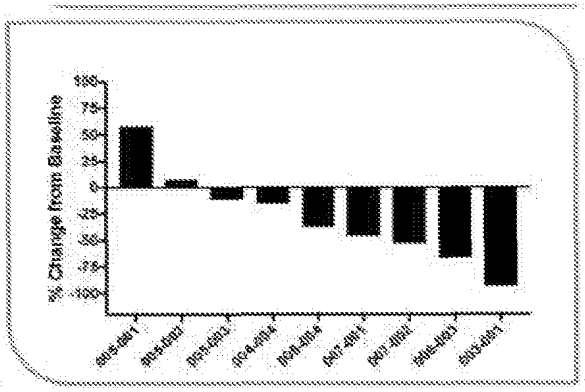



FIG. 15D

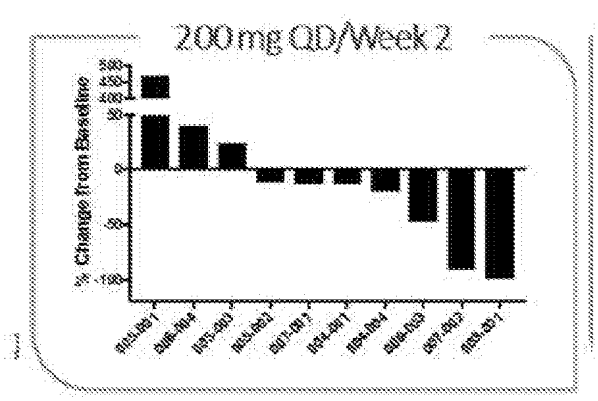



FIG. 16A

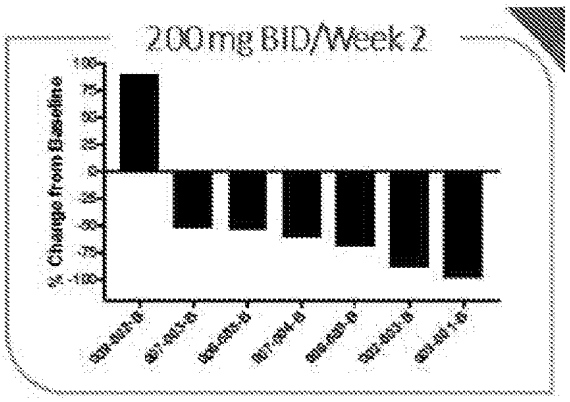



FIG. 16B

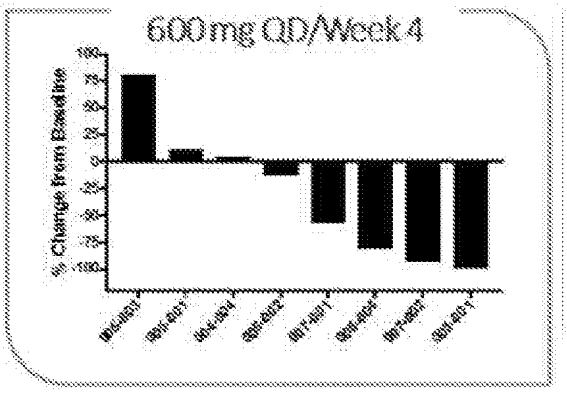



FIG. 16C

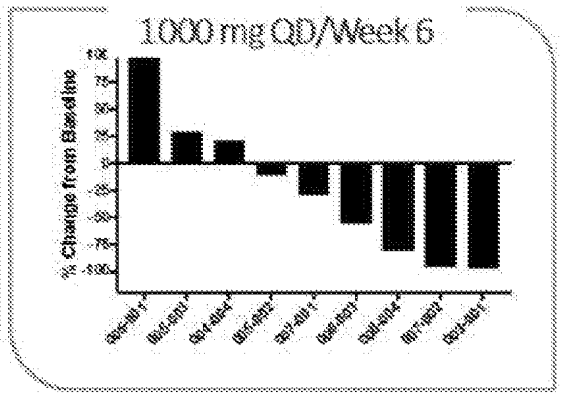



FIG. 16D

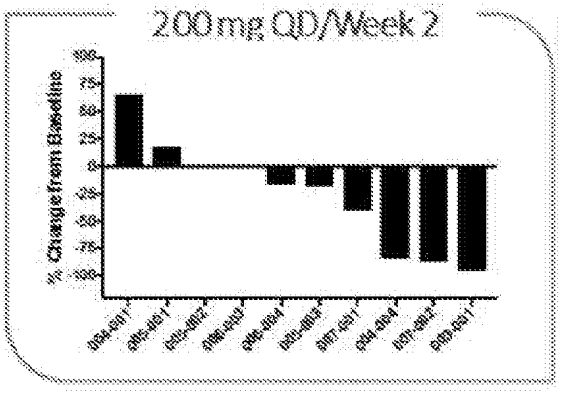



FIG. 17A

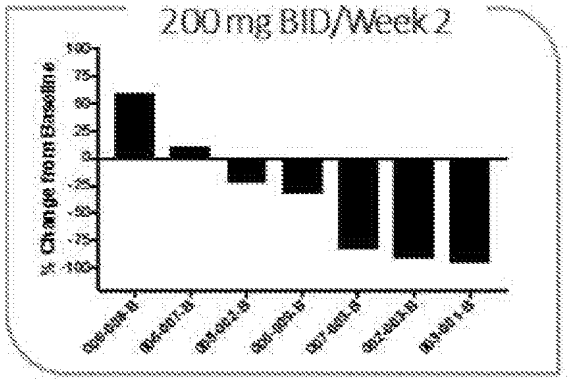



FIG. 17B

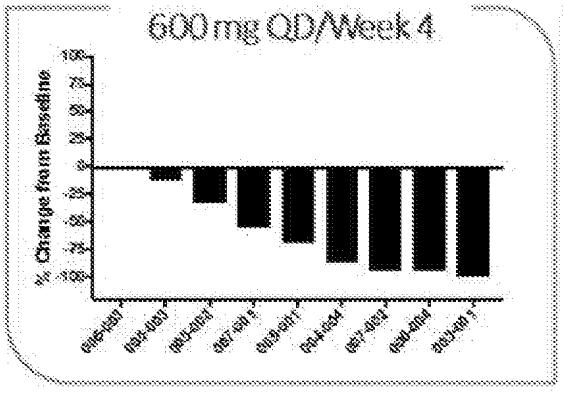



FIG. 17C

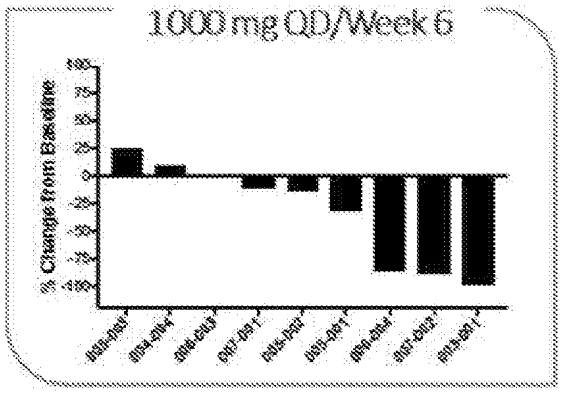



FIG. 17D

## REFERENCES CITED IN THE DESCRIPTION

*This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.*

### Patent documents cited in the description


- US 62663951 **[0001]**
- US 62822815 **[0001]**
- US 4911920 A **[0119]**
- US 5403841 A **[0119]**
- US 5212162 A **[0119]**
- US 4861760 A **[0119]**
- WO 9722596 A **[0129]**
- WO 9730035 A **[0129]**
- WO 9732856 A **[0129]**
- WO 9813354 A **[0129]**
- WO 9902166 A **[0129]**
- WO 0040529 A **[0129]**
- WO 0041669 A **[0129]**
- WO 0192224 A **[0129]**
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- **BERGE et al.** Pharmaceutical Salts. *Journal of Pharmaceutical Science,* 1977, vol. 66, 1-19 **[0079]**
- **LIEBERMAN.** *Pharmaceutical Dosage Forms,* 1992, vol. 1-3 **[0111]**
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- Modified-Release Drug Delivery Technology. Marcel Dekker, Inc, 2008 **[0251]**

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| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 19/043,275 | 01/31/2025 | Alexis HOWERTON | 50535-710.304 |

**CONFIRMATION NO. 5486**

21971
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

**POA ACCEPTANCE LETTER**

*OC00000009292948*

Date Mailed: 08/14/2025

## NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/11/2025.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/atesfai/

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re the Application of:<br><br>Inventors: Alexis Howerton et al.<br><br>Application No.: 19/043,275<br><br>Filing Date: January 31, 2025<br><br>Title: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS | Confirmation No.: 5486<br><br>Art Unit: 1627<br><br>Examiner: Pihonak, Sarah<br><br>Customer No.: 21971<br><br>Certificate of Electronic Filing<br>I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office's electronic filing system to the USPTO on August 15, 2025.<br><br>By: / Colleen Mensching /<br>Colleen Mensching |

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION**

Dear Commissioner:

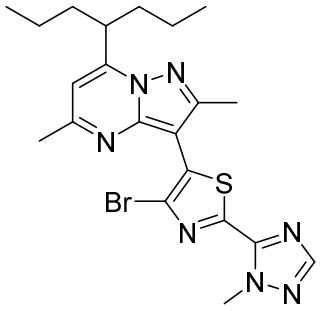
In response to the Non-Final Office Action mailed May 30, 2025, setting an initial due date of August 30, 2025, Applicant respectfully requests reconsideration of the above-referenced application in view of the following amendments and remarks. This response is timely filed.

**Amendments to the Claims** begin on page **2** of this paper.
**Amendments to the Specification** begin on page **6** of this paper.
**Summary of the Interview** begins on page **7** of this paper.
**Remarks** begin on page **8** of this paper.
**Conclusion** begins on page **10** of this paper.

## AMENDMENTS TO THE CLAIMS

### Listing of the Claims

1. (**Currently Amended**) A method of treating an endocrine disorder associated with corticotropin-releasing factor type-1 ($CRF_1$) activity, comprising administering to a subject in need thereof a small molecule $CRF_1$ antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule $CRF_1$ antagonist is: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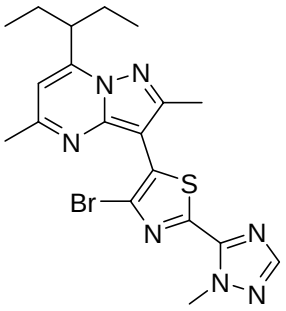
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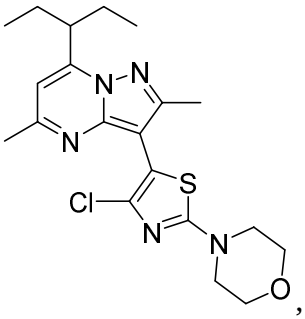
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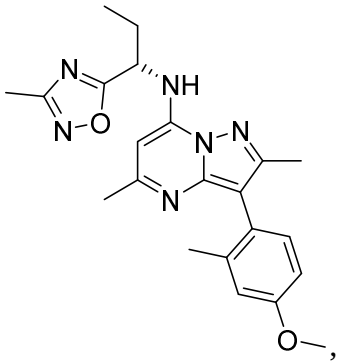
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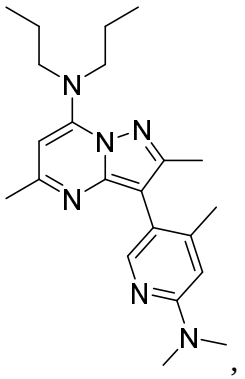
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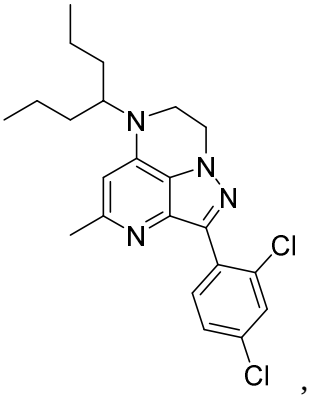
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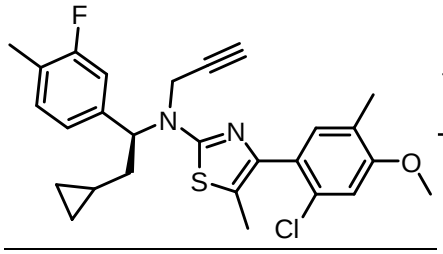
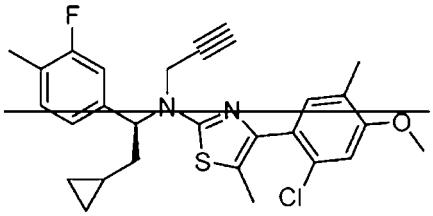
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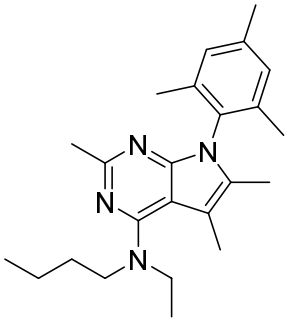
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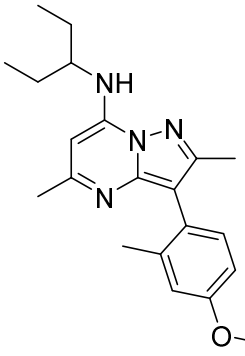
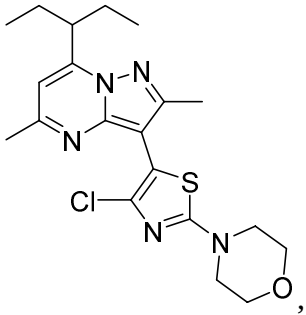

or , or a pharmaceutically acceptable salt thereof,

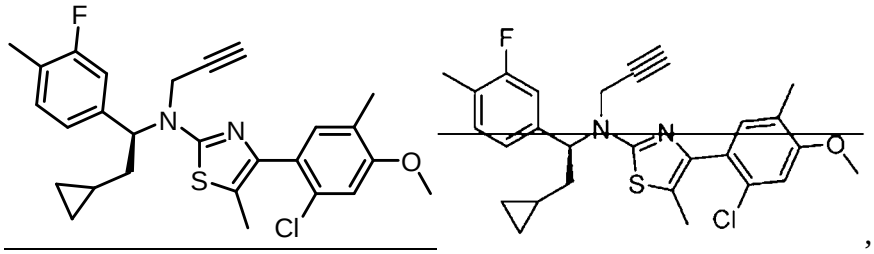
wherein the small molecule $CRF_1$ antagonist is administered to the subject twice per day, and

wherein the subject is in the fed state.

2. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is:


, or a pharmaceutically acceptable salt thereof.

3. (**Currently Amended**) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is:




, or a pharmaceutically acceptable salt thereof.

4. (Original) The method of claim 1, wherein the endocrine disorder associated with $CRF_1$ activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).
5. (Original) The method of claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).
6. (Original) The method of claim 1, wherein the subject is receiving a glucocorticoid in conjunction with the administering of the small molecule $CRF_1$ antagonist.
7. (Original) The method of claim 6, wherein the glucocorticoid comprises beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone, or a combination thereof.
8. (Original) The method of claim 7, wherein the glucocorticoid is hydrocortisone.
9. (Original) The method of claim 1, wherein the subject is an adolescent.
10. (Original) The method of claim 1, wherein the subject is at least 18 years old.
11. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.
12. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 50 mg.
13. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 100 mg.
14. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 200 mg.
15. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 400 mg.
16. (Cancelled)

17. (Cancelled)
18. (Cancelled)
19. (Cancelled)
20. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered orally.
21. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is formulated as a capsule or tablet.
22. (New) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered less than about 6 hours before sleep.
23. (New) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered less than about 3 hours before sleep.
24. (New) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered in the evening.

## AMENDMENTS TO THE SPECIFICATION

Applicant provides herewith both a clean copy and a marked copy of a substitute specification, excluding claims, in compliance with 37 C.F.R. §§ 1.52, 1.121, and 1.125. The amendments follow the Certificate of Correction (submitted on March 12, 2025, and accepted by the U.S. Patent Office on June 17, 2025) for U.S. Pat. No. 11,304,950.

Applicant respectfully requests that the specification of record be replaced with the substitute specification filed herewith.

## SUMMARY OF THE INTERVIEW

Applicant is appreciative of Examiner Pihonak for extending the courtesy of a videoconference interview with Applicant's representatives, Victoria Cheng (Reg. No. 79,641) and Kaia Parenti (Reg. No. 81,050), on August 6, 2025.

During the interview, proposed claim amendments were discussed. Agreement was reached that the amendments would overcome the novelty and obviousness rejections.

## REMARKS

Claims 1-21 were pending prior to entry of the amendments presented in this response. Claims 1 and 3 are herein amended. Claim 1 has been amended to incorporate the subject matter of claims 17 and 19. New claims 22-24 have been added, for which support can be found in the as-filed specification (now published as U.S. Pub. No. 2025-0177404), at least at ¶¶ [0263], [0274]. Claims 16-19 are herein canceled without prejudice or disclaimer. No new matter is believed to be added by any of these amendments.

### 35 U.S.C. § 102 Novelty

Claims 1, 3, 5-8, 10-12, 15-16, and 20-21 are rejected as allegedly being anticipated by Grigoridadis (U.S. Pub. No. 2017-0020877; hereafter "Grigoriadis"), as evidenced by El-Maouche et. al., *Lancet*, vol. 309, pp. 2194-2210, publ. 2017 (hereafter "El-Maouche").

Applicant has amended claim 1 to incorporate the limitations of dependent claims 17 and 19, which were not rejected as lacking novelty. As such, Applicant respectfully submits amended claim 1 is novel over the cited reference and requests withdrawal of the novelty rejection. Similarly, Applicant submits claims 3, 5-8, 10-12, 15-16, and 20-21 are also novel over the cited reference by virtue of their dependencies on amended claim 1.

### 35 U.S.C. § 103 Obviousness

Claims 9 and 13-14 are rejected as allegedly lacking nonobviousness over Grigoridadis, as evidenced by El-Maouche et. al., Lancet, vol. 309, pp. 2194-2210, publ. 2017, as applied to claims 1, 3, 5-8, 10-12, 15-16, and 20-21. Claims 1-2, 10-16, and 20 are rejected as allegedly lacking nonobviousness over Chen et. al. (U.S. Pub. No. 2010-0222339; hereafter "Chen").

Applicant has amended claim 1 to incorporate the limitations of dependent claims 17 and 19, which were not rejected as lacking nonobviousness. As such, Applicant respectfully submits amended claim 1 is nonobvious over the cited references and requests withdrawal of the obviousness rejection. Similarly, Applicant submits claims 3, 5-8, 10-12, 15-16, and 20-21 are also nonobvious over the cited references by virtue of their dependencies on amended claim 1.

**Double Patenting**

Claims 1-17 and 20-21 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-19 of U.S. Pat. No. 11,304,950 B2. Claims 1-3, 6-7, 9-17, and 20-21 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-18 and 20-21 of U.S. Pat. No. 11,858,932 B2 in view of Markopoulos et. al., *J. Clin. Endocrinol. Metab.*, vol. 96(3), pp. 623-631, publ. 2011 (hereafter "Markopoulos") and over claims 1-18 and 20-21 of U.S. Pat. No. 12,098,152 B2 in view of Markopoulos. Claims 1-2, 5-17, and 20-21 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over (1) claims 1-4, 7-9, 11-17, and 20-21 of U.S. Pat. No. 11,311,549 B2; (2) claims 1-4, 7-9, 11-17, 19-24, and 26-27 of U.S. Pat. No. 11,344,557 B2; and (3) claims 1-4, 7-9, 11, and 14-21 of U.S. Pat. No. 11,351,177 B2.

Applicant has amended claim 1 to incorporate the subject matter of claims 17 and 19, which were not rejected under nonstatutory double patenting over the cited patents above. As such, Applicant respectfully requests withdrawal of the rejection and favorable reconsideration.

*Provisional Nonstatutory Double Patenting*

Claims 1-2 and 5-19 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 181-188, 194-195, 198-199, 202, and 204 of copending application 18/078,649. Claims 1-5, 9-15, and 17-21 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 72-91 of copending application 18/941,832. Claims 1-5, 9-17, and 20-21 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-19 of copending application 19/043,303. Claims 1-3, 5, and 9-21 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-21 of copending application 19/043,264.

Applicant has amended claim 1 to incorporate the subject matter of claims 17 and 19, which was not provisionally rejected under nonstatutory double patenting over claims in U.S. App. No. 19/043,303. As such, Applicant respectfully requests withdrawal of the rejection and favorable reconsideration.

Without acquiescing to the rejection, Applicant submits herewith a terminal disclaimer over U.S. App. Nos. 18/078,649, 18/941,832, and 19/043,264.

## CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (858)-350-2240.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 50535-710.304).

Respectfully submitted,

Date: August 15, 2025

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79,641

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
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# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **08/15/2025 06:11:36 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | Colleen Mensching |
| PATENT CENTER # | 71882153 | FILING DATE | 01/31/2025 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Victoria Cheng |

## Documents

**TOTAL DOCUMENTS: 7**

| DOCUMENT | | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|---|
| Spruce 50535-710.304 - Substitute Specification clean.pdf | | 113 | Specification | 1109 KB |
| Spruce 50535-710.304 - Substitute Specification marked.pdf | | 113 | Specification | 1118 KB |
| Spruce 50535-710.304 - NFOA Response.pdf | | 10 | - | 212 KB |
| Spruce 50535-710.304 - NFOA Response-A....pdf | (1-1) | 1 | Amendment/Request for Reconsideration-After Non-Final Rejection | 110 KB |
| Spruce 50535-710.304 - NFOA Response-CLM.pdf | (2-5) | 4 | Claims | 161 KB |

| | | | | |
|---|---|---|---|---|
| Spruce 50535-710.304 - NFOA Response-SPEC.pdf | (6-6) | 1 | Specification | 108 KB |
| Spruce 50535-710.304 - NFOA Response-INTRVIEW.APP.pdf | (7-7) | 1 | Applicant summary of interview with examiner | 108 KB |
| Spruce 50535-710.304 - NFOA Response-REM.pdf | (8-10) | 3 | Applicant Arguments/Remarks Made in an Amendment | 151 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| Spruce 50535-710.304 - Substitute Specification clean.pdf | 5D678A90C494E0412BB4EF10A1CE181592F94C4F0F0177C6D379A3E511F8538F69F27D6D74A5FE74BC1113FC76BF82C690AC7FB7CF6B8770AA333FB1E76C9EA9 |
| Spruce 50535-710.304 - Substitute Specification marked.pdf | 8141D51A374733FE4D0262B7FA77172CAAF34D6BBFE2CE3B22D0809ED33F15BB98EB2526C657EEF6B8A487A896FF874F9EDB4C975B22D15958F73A78ECEBE67A |
| Spruce 50535-710.304 - NFOA Response.pdf | B0325B0FE219794D7D2EB7EC3ADEFA380C53917EF5727E1C0275D1681BFBD4BEDA00CB3BABE8F36110A8F9D1AD89C7F3D81CD0A2D767DC6D84B28A61B8914836 |
| Spruce 50535-710.304 - NFOA Response-A....pdf | CAED5D9E67ADF536270E71102468F155D5E364B6E1871273B60A9929ED81B639D55D9BFFAEB63E96986719000698CE2AD5EE53BCCB23A248DF82F3D1B561F52E |
| Spruce 50535-710.304 - NFOA Response-CLM.pdf | 92879AFF85D40C3CE5D184447B2CEA16ACC44F54BB9B38FA097796CF3571A9A71B295601A53FE48815B8A2B9A59CA16118ED4B97B604C836ED1671B133122074 |
| Spruce 50535-710.304 - NFOA Response-SPEC.pdf | 6C96B3F7523E3F60B2B8A89D06ABC0A1A52AB09A53F32F825B24DB51D99312A43F237CA30C6A310310B770C8A021F7A9F31E2E3A9E37FF17C1B2219F466B4122 |
| Spruce 50535-710.304 - NFOA Response-INTRVIEW.APP.pdf | 1D614F849010B6794FC47E301DA39F16E467FEF2F9A29622AF4C32E82CEA79F2888F09166E2CA7A509A787A3459024AEDCC5CD64AA6292A6A01DBFB8348295D6 |
| Spruce 50535-710.304 - NFOA Response-REM.pdf | C214643E676C230D7B95045E1E8350AE666457EF5358A8DD614BA7BF913842F9759D45943B45D592FF53C2BAECBEE63F396961702F5AAEAF0DA40FCB13FCA96F |

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# METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## CROSS-REFERENCE

**[0001]** This application is a continuation of U.S. Application No. 18/941,832, filed November 8, 2024, which is a continuation of U.S. Application No. 17/667,285, filed on February 8, 2022, which is a continuation of U.S. Application No. 17/081,694 filed on October 27, 2020, which issued as U.S. Pat. No. 11,304,950 on April 19, 2022, and which is a continuation of International Application No. PCT/US2019/029486 filed on April 26, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed April 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019, each of which is entirely incorporated herein by reference.

## BACKGROUND

**[0002]** Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

**[0003]** CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

**[0004]** Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, *inter alia*, are solutions to these and other problems in the art.

## SUMMARY

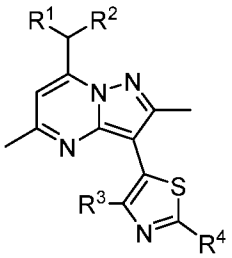
**[0005]** Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

**[0006]** Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

**[0007]** One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

**[0008]** In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

**[0009]** One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):

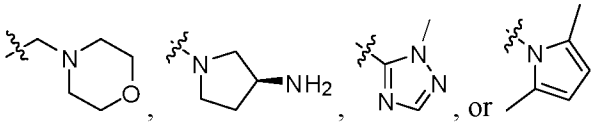



(I), or a pharmaceutically acceptable salt thereof,

wherein:

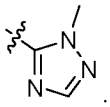
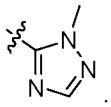
$R^1$ and $R^2$ are independently ethyl or n-propyl;

$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

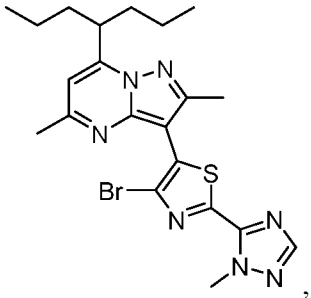
$R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, 

, or ;

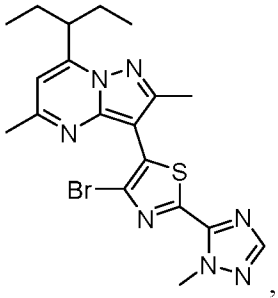
$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

**[0010]** In some embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl. In some embodiments, $R^3$ is Cl, Br, or methyl. In some embodiments, $R^4$ is Br, $R^aR^bN$–, pyridin-4-yl, morpholin-4-yl, or . In some embodiments, $R^4$ is morpholin-4-yl or .

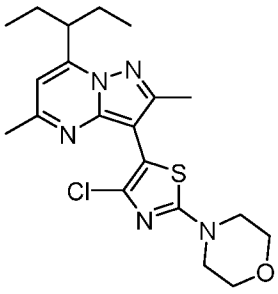
**[0011]** In some embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$– and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl. In some embodiments, the compound is

, or a pharmaceutically acceptable salt thereof.

**[0012]** In some embodiments, the compound is

, or a pharmaceutically acceptable salt thereof.

**[0013]** In some embodiments, the compound is

, or a pharmaceutically acceptable salt thereof.

**[0014]** In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

**[0015]** In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically

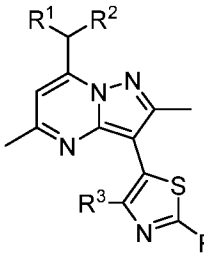
acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

**[0016]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

**[0017]** In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

**[0018]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

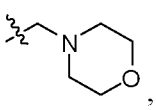
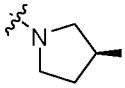
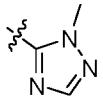
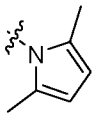
**[0019]** One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:


(I), or a pharmaceutically acceptable salt thereof,

wherein:

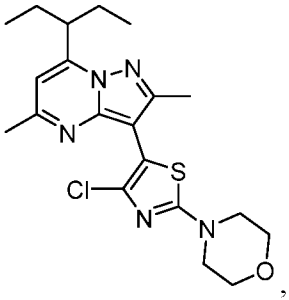
$R^1$ and $R^2$ are independently ethyl or n-propyl;

$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

$R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or ;

$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

**[0020]** In some embodiments, the compound of Formula (I) has the structure:


, or a pharmaceutically acceptable salt thereof.

**[0021]** In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0022]** In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about

265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

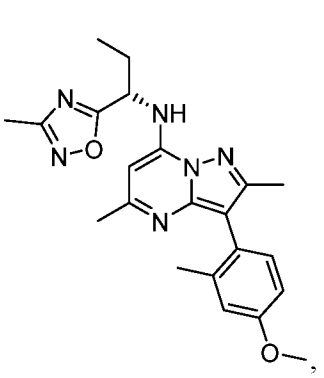
**[0023]** In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

**[0024]** In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

**[0025]** In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

**[0026]** In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

**[0027]** In some embodiments, the additional chemotherapeutic agent is another $CRF_1$ antagonist. In some embodiments, the $CRF_1$ antagonist is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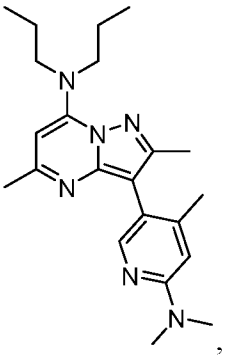
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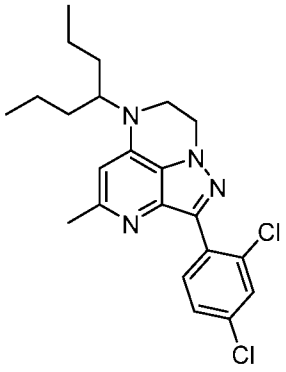
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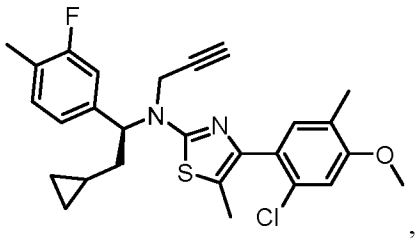
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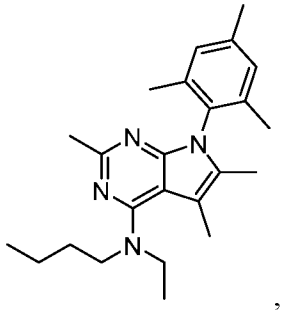
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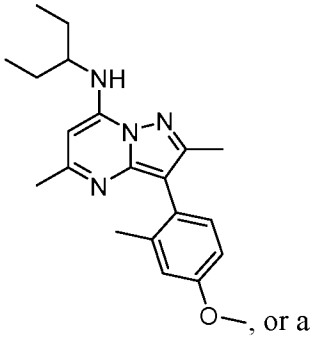
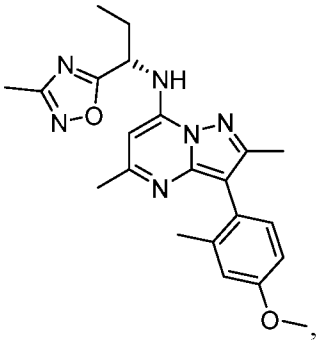

, or a pharmaceutically acceptable salt thereof.

**[0028]** In some embodiments, the $CRF_1$ antagonist is


, or a pharmaceutically acceptable salt thereof.

**[0029]** In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

**[0030]** In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

**[0031]** In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with

administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0032]** In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the $CRF_1$ antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0033]** In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0034]** Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

## INCORPORATION BY REFERENCE

**[0035]** All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0036]** The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

**[0037] FIG. 1A-1B**. A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics **(A).** A schematic representation of inhibition of $CRF_1$ with a $CRF_1$ antagonist (Compound 1) **(B)**.

**[0038] FIG. 2**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a $CRF_1$ antagonist (Compound 1).

**[0039] FIG. 3**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a $CRF_1$ antagonist (Compound 1).

**[0040] FIG. 4**. Graphic representation of patient-level response (measuring ACTH levels) to a $CRF_1$ antagonist (Compound 1).

**[0041] FIG. 5A-5B**. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a $CRF_1$ antagonist [Patient 10 **(A)**; Patient 8 **(B)**].

**[0042] FIG. 6**. Graphic representation of patient-level response (measuring 17-OHP levels) to a $CRF_1$ antagonist (Compound 1).

**[0043] FIG. 7A-7B**. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to a $CRF_1$ antagonist [Patient 10 **(A)**; Patient 8 **(B)**].

**[0044] FIG. 8**. Graphic representation of patient-level response (measuring androstenedione levels) to a $CRF_1$ antagonist (Compound 1).

**[0045] FIG. 9A-9B**. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a $CRF_1$ antagonist (Compound 1) [Patient 10 **(A)**; Patient 8 **(B)**].

**[0046] FIG. 10A-10B**. Images of a patient with TART pre-treatment with a $CRF_1$ antagonist (Compound 1) **(A)** and 6-weeks post-treatment with a $CRF_1$ antagonist (Compound 1) **(B)**.

**[0047] FIG. 11A-11B**. Graphic representation of an *in vitro* binding assay of a $CRF_1$ antagonist (Compound 1); $^{125}$I-sauvagine binding to rat cerebellar membranes one hour after oral administration of increasing Compound 1 doses **(A)** and *in vivo* inhibition of CRF-induced activity after treatment with a $CRF_1$ antagonist; Compound 1 (oral, 10 mg/kg) **(B)**.

**[0048] FIG. 12A-12B**. Graphic representation of ACTH levels (A) and 17-OHP levels (B) after treatment with a $CRF_1$ antagonist.

**[0049] FIG. 13**. Graphic representation of hormone responses after treatment with a $CRF_1$ antagonist (Compound 1).

**[0050] FIG. 14** depicts the proof of concept and escalating QD dosing at 10 pm for Cohort A and the single dose level and BID dosing at 10 am and 10 pm for Cohort B.

**[0051] FIG. 15A-15D** are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

**[0052] FIG. 16A-16D** are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

**[0053] FIG. 17A-17D** are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

## DETAILED DESCRIPTION

**[0054]** While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

### I. Definitions

**[0055]** The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

**[0056]** Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

**[0057]** The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., $C_1$-$C_{10}$ means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

**[0058]** The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms,

with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

**[0059]** The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

**[0060]** Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

**[0061]** The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

**[0062]** The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo($C_1$-$C_4$)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

**[0063]** The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

**[0064]** The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and

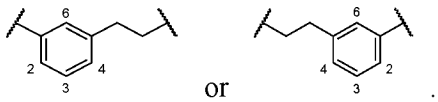
the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

**[0065]** Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

**[0066]** The symbol " " denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

**[0067]** The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

**[0068]** The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:

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**[0069]** An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -CHO, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2CH_3$ $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $–NHNH_2$, $–ONH_2$, $–NHC(O)NHNH_2$, substituted or unsubstituted $C_1$-$C_5$ alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

**[0070]** Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

**[0071]** Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', $-NR"C(O)_2R'$, -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, $–NR'NR"R"'$, $–ONR'R"$, $–NR'C(O)NR"NR"'R""$, -CN, $-NO_2$, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R"', and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include

groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -$CF_3$ and -$CH_2CF_3$) and acyl (e.g., -$C(O)CH_3$, -$C(O)CF_3$, -$C(O)CH_2OCH_3$, and the like).

**[0072]** Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, -SiR'R"R'", -OC(O)R', -C(O)R', -$CO_2$R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", -NR"$C(O)_2$R', -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'", -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', –NR'NR"R'", –ONR'R", –NR'C(O)NR"NR'"R"", -CN, -$NO_2$, -R', -$N_3$, -$CH(Ph)_2$, fluoro($C_1$-$C_4$)alkoxy, and fluoro($C_1$-$C_4$)alkyl, -NR'$SO_2$R", -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R'", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" groups when more than one of these groups is present.

**[0073]** Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the

heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

**[0074]** Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

**[0075]** Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C"R"R"')_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R", and R"' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

**[0076]** As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

**[0077]** A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -$CF_3$, -CN, -OH, -$NH_2$, -COOH, -$CONH_2$, -$NO_2$, -SH, -$SO_3H$, -$SO_4H$, -$SO_2NH_2$, –$NHNH_2$, –$ONH_2$, –NHC=(O)$NHNH_2$, –NHC=(O) $NH_2$, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -$OCF_3$, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, -$CF_3$, -CN, -OH, -$NH_2$, -COOH, -$CONH_2$, -$NO_2$, -SH, -$SO_3H$, -$SO_4H$, -$SO_2NH_2$, –$NHNH_2$, –$ONH_2$, –NHC=(O)$NHNH_2$, –NHC=(O) $NH_2$, -$NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, -$OCF_3$, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, -$CF_3$, -CN, -OH, -$NH_2$, -COOH, -$CONH_2$, -$NO_2$, -SH, -$SO_3H$, -$SO_4H$, -$SO_2NH_2$, –$NHNH_2$, –$ONH_2$, –NHC=(O)$NHNH_2$, –NHC=(O) $NH_2$, -$NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, -$OCF_3$, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, -$CF_3$, -CN, -OH, -$NH_2$, -COOH, -$CONH_2$, -$NO_2$, -SH, -$SO_3H$, -$SO_4H$, -$SO_2NH_2$, –$NHNH_2$, –$ONH_2$, –NHC=(O)$NHNH_2$, –NHC=(O) $NH_2$, -$NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, -$OCF_3$, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

**[0078]** A “size-limited substituent” or “ size-limited substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_{20}$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_8$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

**[0079]** A “lower substituent” or “ lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_8$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, each

substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

**[0080]** In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

**[0081]** In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted $C_1$-$C_{20}$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_8$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted $C_1$-$C_{20}$ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted $C_3$-$C_8$ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted $C_6$-$C_{10}$ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

**[0082]** In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_8$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some

embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted $C_1$-$C_8$ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted $C_3$-$C_7$ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted $C_6$-$C_{10}$ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

**[0083]** Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

**[0084]** As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

**[0085]** The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

**[0086]** It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

**[0087]** Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

**[0088]** Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a

deuterium or tritium, or the replacement of a carbon by $^{13}C$- or $^{14}C$-enriched carbon are within the scope of this invention.

**[0089]** The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium ($^{3}H$), iodine-125 ($^{125}I$), or carbon-14 ($^{14}C$). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

**[0090]** It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

**[0091]** "Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

**[0092]** The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted $C_1$-$C_{20}$ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted $C_1$-$C_{20}$ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

**[0093]** Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple $R^{13}$ substituents are present, each $R^{13}$ substituent may be distinguished as $R^{13A}$, $R^{13B}$, $R^{13C}$, $R^{13D}$, etc., wherein each of $R^{13A}$, $R^{13B}$, $R^{13C}$, $R^{13D}$, etc. is defined within the scope of the definition of $R^{13}$ and optionally differently.

**[0094]** A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

**[0095]** Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

**[0096]** The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic,

methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

**[0097]** Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

**[0098]** The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

**[0099]** In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

**[0100]** Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In

general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

**[0101]** "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of a compound to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

**[0102]** The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

**[0103]** A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

**[0104]** The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and "protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and

homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

**[0105]** A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, *e.g.*, in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

**[0106]** "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

**[0107]** The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

**[0108]** As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

**[0109]** The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist. In embodiments, an agonist is a molecule that interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

**[0110]** As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

**[0111]** The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

**[0112]** The terms "corticotropin-releasing factor type-1," "$CRF_1$," "corticotropin-releasing hormone receptor 1," and "CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms include any recombinant or naturally-occurring form of $CRF_1$ variants thereof that maintain $CRF_1$ activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of $CRF_1$ variants (e.g., frameshift mutations) thereof that maintain $CRF_1$ activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype $CRF_1$). In

embodiments, the $CRF_1$ protein encoded by the *CRHR1* gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

**[0113]** The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.*).

**[0114]** The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

**[0115]** As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer,

premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

**[0116]** The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

**[0117]** "Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

**[0118]** "Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

**[0119]** The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic

leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

**[0120]** The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

**[0121]** The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

**[0122]** The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma,

comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

**[0123]** The terms “treating” or “treatment” refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term “treating” and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

**[0124]** “Treating” or “treatment” as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject’s condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent

of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (*e.g.*, ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

**[0125]** "Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

**[0126]** The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

**[0127]** "Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

**[0128]** An "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a

"therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see*, *e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a CRF1 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

**[0129]** For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

**[0130]** Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based

on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

**[0131]** The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

**[0132]** The terms "QD," "qd," and "q.d." refer to once a day, i.e., a drug or therapeutic agent is administered once a day for the duration of the therapeutic regimen.

**[0133]** The terms "BD," "bd," and "b.i.d." refer to twice a day, i.e., a drug or therapeutic agent is administered two times a day for the duration of the therapeutic regimen.

**[0134]** The terms "QID," "qid," and "q.i.d." refer to three times a day, i.e., a drug or therapeutic agent is administered three times a day for the duration of the therapeutic regimen.

**[0135]** Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

**[0136]** As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.,* a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.,* buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.,* intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is

administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.,* by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

**[0137]** By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

**[0138]** For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

**[0139]** Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

**[0140]** The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

**[0141]** In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

**[0142]** The compounds described herein can be administered to treat a fertility disease or disorder and/or cancer. In this regard, the compounds disclosed herein may be administered

either alone to treat such diseases or disorders or may be co-administered with another therapeutic agent to treat such diseases or disorders.

**[0143]** The compounds disclosed herein may be co-administered with an agonist or antagonist of $CRF_1$ function. The compounds described herein can be co-administered with conventional anti-cancer/chemotherapeutic.

**[0144]** "Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (*e.g.,* cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (*e.g.,* 5- azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (*e.g.,* vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (*e.g.,* irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.,* doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin,

all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor

inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain

antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including recombinant interleukin II, or rlL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine;

mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-

39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, lnanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, lsoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (*e.g.,* dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (*e.g.,* Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (*e.g.,* anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (*e.g.,* anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (*e.g.,* anti-CD20 monoclonal antibody conjugated to $^{111}$In, $^{90}$Y, or $^{131}$I, *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa ™), erlotinib (Tarceva ™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™),

vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

**[0145]** "Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

**[0146]** The compounds disclosed herein may be co-administered with an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5.alpha.-reductase such as finasteride; (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoli- n-4-amine (gefitinib, AZD 1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazoli- n-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte

growth factor family; (v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin .alpha.v.beta.3 function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

**[0147]** In embodiments, the compounds disclosed herein can be co-administered with an antibody, such as a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax I1-15) or antibody modulating Ig function such as anti-IgE (for example omalizumab).

**[0148]** In embodiments, treatment of cancer includes administration of an effective amount of at least two of the following: a CRF1 inhibitor, an inhibitor of the PD-L1/PD-1 pathway, an inhibitor of CTLA-4, an agonistic antibody of CD137 (4-1BB). In some embodiments, the method may comprise the use of two or more combinations.

**[0149]** In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as $^{47}Sc$, $^{64}Cu$, $^{67}Cu$, $^{89}Sr$, $^{86}Y$, $^{87}Y$, $^{90}Y$, $^{105}Rh$, $^{111}Ag$, $^{111}In$, $^{117m}Sn$, $^{149}Pm$, $^{153}Sm$, $^{166}Ho$, $^{177}Lu$, $^{186}Re$, $^{188}Re$, $^{211}At$, and $^{212}Bi$, optionally conjugated to antibodies directed against tumor antigens.

**[0150]** In addition, a $CRF_1$ inhibitor may be combined with the therapeutic administration of immune cells, sometimes referred to as adoptive cell transfer. These cells may be cells from the patient, a genetically related or unrelated donor, they may be genetically modified (e.g. CAR-T cells, NK cells, etc), cell lines, genetically modified cell lines and live or dead versions of the

above. CRF1 inhibitors may also be combined with vaccines of any kind (e.g. protein/peptide, viral, bacterial, cellular) to stimulate immune responses to cancer.

**[0151]** The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

**[0152]** The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

**[0153]** The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein may be administered once daily until study reached endpoint. The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein may be administered at least three times but in some studies four or more times depending on the length of the study and/or the design of the study.

**[0154]** The methods disclosed herein may be used in combination with additional cancer therapy. In some embodiments, the distinct cancer therapy comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy. In some embodiments, the cancer is a chemotherapy-resistant or radio-resistant cancer.

**[0155]** A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaroytic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (*e.g.*, spodoptera) and

human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

**[0156]** "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

**[0157]** The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. In some embodiments, a CRF1 associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with $CRF_1$ (e.g. an endocrine disorder, a cancer including but not limited to TART or OART). A $CRF_1$ modulator is a compound that increases or decreases the activity or function or level of activity or level of function of $CRF_1$. A modulator may act alone, or it may use a cofactor, e.g., a protein, metal ion, or small molecule. Examples of modulators include small molecule compounds and other bioorganic molecules. Numerous libraries of small molecule compounds (e.g., combinatorial libraries) are commercially available and can serve as a starting point for identifying a modulator. The skilled artisan is able to develop one or more assays (e.g., biochemical or cell-based assays) in which such compound libraries can be screened in order to identify one or more compounds having the desired properties; thereafter, the skilled medicinal chemist is able to optimize such one or more compounds by, for example, synthesizing and evaluating analogs and derivatives thereof. Synthetic and/or molecular modeling studies can also be utilized in the identification of an activator.

**[0158]** The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms "modulate", "modulation" and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of $CRF_1$, either directly or indirectly, relative to the absence of the molecule.

**[0159]** The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, an endocrine disorder, a disease associated with $CRF_1$ activity, a $CRF_1$ associated disease (e.g., testicular

adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, an endocrine disorder associated with $CRF_1$ activity or function may be an endocrine disorder that results (entirely or partially) from aberrant $CRF_1$ function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or an endocrine disorder wherein a particular symptom of the disease is caused (entirely or partially) by aberrant $CRF_1$ activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, an endocrine disorder associated with $CRF_1$ activity or function or a $CRF_1$ associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., $CRF_1$ modulator, $CRF_1$ inhibitor, or $CRF_1$ antagonist), in the instance where increased $CRF_1$ activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART). For example, an endocrine disorder associated with $CRF_1$ activity or function or a $CRF_1$ associated endocrine disorder, may be treated with an $CRF_1$ modulator or $CRF_1$ inhibitor, in the instance where increased $CRF_1$ activity or function (e.g. signaling pathway activity) causes the disease.

**[0160]** The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

**[0161]** The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propogated to other signaling pathway components. For example, binding of a $CRF_1$ with a compound as described herein may reduce the level of a product of the $CRF_1$ catalyzed reaction or the level of a downstream derivative of the product or binding may reduce the interactions between the $CRF_1$ or a reaction product and downstream effectors or signaling pathway components (e.g., MAP kinase pathway), resulting in changes in cell growth, proliferation, or survival.

**[0162]** As used herein, the terms "corticotropin-releasing factor type-1," "$CRF_1$," "corticotropin-releasing hormone receptor 1," and "CHHR1" and all other related art-accepted

terms, many of which are set forth below, refer to a compound capable of modulating, either directly or indirectly, the $CRF_1$ receptor in an *in vitro* assay, an *in vivo* model, and/or other means indicative of therapeutic efficacy. The terms also refer to a compound that exhibits at least some therapeutic benefit in a human subject.

**[0163]** The phrase "in a sufficient amount to effect a change" means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject's feeling of well-being).

**[0164]** The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

**[0165]** "Substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

**[0166]** The terms "specifically binds" and "selectively binds," when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample. The antibody, or binding composition derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen, or a variant or mutein thereof, with an affinity that is at least two-fold greater, at least 10-times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antibody, or binding composition derived therefrom. In embodiments, the antibody will have an affinity that is greater than about $10^9$ liters/mol, as determined by, e.g., Scatchard analysis (Munsen, et al. (1980) Analyt. Biochem. 107:220-239).

**[0167]** The terms "DNA," "nucleic acid," "nucleic acid molecule," "polynucleotide" and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, messenger RNA (mRNA),

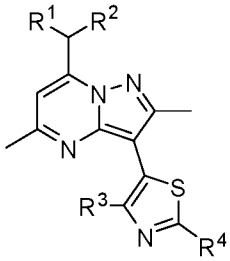
complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

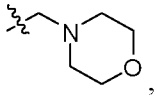
**[0168]** As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced (e.g., muteins); for example, the change is generated in the laboratory by human intervention ("hand of man"). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

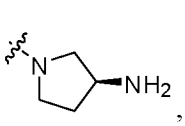
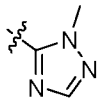
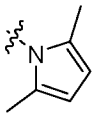
**[0169]** The term "muteins" as used herein refers broadly to mutated recombinant proteins. These proteins usually carry single or multiple amino acid substitutions and are frequently derived from cloned genes that have been subjected to site-directed or random mutagenesis, or from completely synthetic genes.

## II. Compounds

**[0170]** In an aspect provided herein, is a compound of Formula (I):

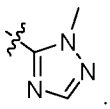


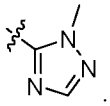
, or a pharmaceutically acceptable salt thereof. $R^1$ and $R^2$ are independently ethyl or n-propyl. $R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. $R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, ,

, , or . $R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–In embodiments, the inhibitor forms an irreversible bond with the amino acid residue. In embodiments, the bond is a covalent bond.

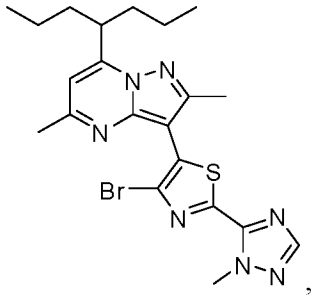
**[0171]** In certain embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl.

**[0172]** In certain embodiments, $R^3$ is Cl, Br, or methyl.

**[0173]** In certain embodiments, $R^4$ is Br, $R^aR^bN$–, pyridin-4-yl, morpholin-4-yl, or .

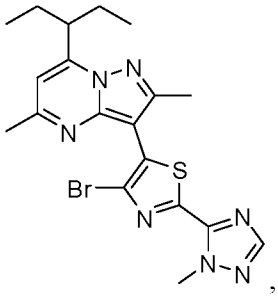
**[0174]** In certain embodiments, $R^4$ is morpholin-4-yl or .

**[0175]** In certain embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$– and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

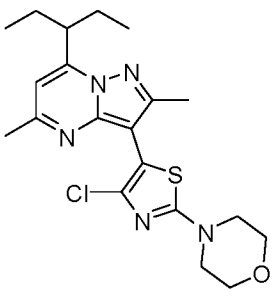


**[0176]** In certain embodiments, the compound is , or a pharmaceutically acceptable salt thereof.

**[0177]** In certain embodiments, the compound is

, or a pharmaceutically acceptable salt thereof.

**[0178]** In certain embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

**[0179]** In one aspect described herein, there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

**[0180]** In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof; and repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of said astressin.

**[0181]** In one aspect described herein, there is a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

**[0182]** In one aspect described herein, there is a method of improving quality of life in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

## III. Pharmaceutical Compositions

**[0183]** In an aspect, there is provided a pharmaceutical composition, including a compound as described herein, including embodiments, or the structural Formula (I), and a pharmaceutically acceptable excipient.

**[0184]** The compounds (e.g., $CRF_1$ inhibitors/antagonists) of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are "pharmaceutical compositions" comprising a compound (e.g., $CRF_1$ inhibitor(s)/ antagonist(s)) and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In certain embodiments, the compound (e.g., $CRF_1$ inhibitor/antagonist) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

**[0185]** In one aspect described herein, there is a pharmaceutical composition in the form of a capsule comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a pharmaceutical composition in the form of a tablet comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

**[0186]** The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

**[0187]** The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of $CRF_1$ function) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

**[0188]** The tablets, capsules and the like suitable for oral administration may be uncoated or coated to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for

controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly(methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

**[0189]** Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

**[0190]** Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

**[0191]** Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

**[0192]** Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting

agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

**[0193]** The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

**[0194]** The pharmaceutical compositions typically comprise a therapeutically effective amount of a $CRF_1$ inhibitor/antagonist contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

**[0195]** After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container

(e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

**[0196]** Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a $CRF_1$ inhibitor/antagonist, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

**[0197]** Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., $CRF_1$ inhibitor/antagonist) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

**[0198]** The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

**[0199]** The present disclosure contemplates the administration of the compound (e.g., $CRF_1$ inhibitor/antagonist) in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

**[0200]** The compound (e.g., $CRF_1$ inhibitor/antagonist) contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

## IV. Methods

**[0201]** In certain embodiments, provided herein are methods for treating or preventing a disease comprising administering an effective amount of a compound of Formula (I), or an isotopic variant thereof or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

**[0202]** In one embodiment, provided herein are methods for treating or preventing a tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a benign tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a malignant tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal rest tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

**[0203]** In one embodiment, provided herein are methods for treating or preventing infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing male infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm count, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm motility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm morphology, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are

methods for treating or preventing female infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

**[0204]** In one embodiment, provided herein are methods for treating or preventing a proliferative or hyperproliferative disease or disorder, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a cancer of the breast, skin, prostate, cervix, uterus, ovary, testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system.

**[0205]** In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenstrom's macroglobulinemia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, aligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mutinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and

inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prol actin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonserninoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcorna; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but

not limited to, renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (*See* Fishman *et al.*, 1985, *Medicine*, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy *et al.*, 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

**[0206]** Depending on the disorder, disease, or condition to be treated, and the subject's condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration as described elsewhere herein.

**[0207]** The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. Recommended routes of administration for the second active agents are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

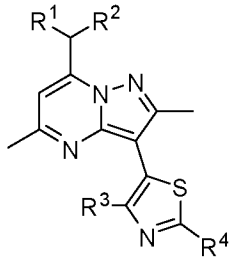
**[0208]** In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

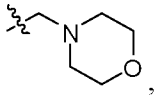
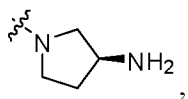
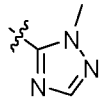
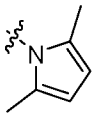
**[0209]** In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

**[0210]** In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

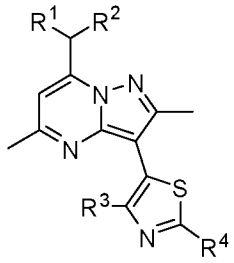
**[0211]** In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

**[0212]** In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):



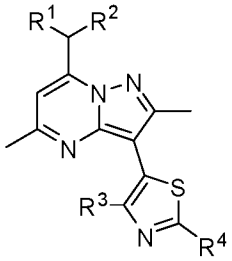
, or a pharmaceutically acceptable salt thereof. $R^1$ and $R^2$ are independently ethyl or n-propyl. $R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. $R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or . $R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

**[0213]** In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



, or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments.

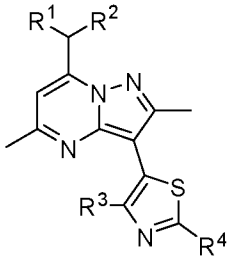
**[0214]** In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):



, or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 60% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 70% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 80% of the subjects demonstrate reduction in ACTH. In embodiments, at least about 10% of subjects were in the standard or normal range for ACTH after treatment.

**[0215]** In embodiments, at least about 20% of subjects were in the standard or normal range for ACTH after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for ACTH after treatment. In certain embodiments, ACTH levels are decreased or reduced within about 30 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 1 hour post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

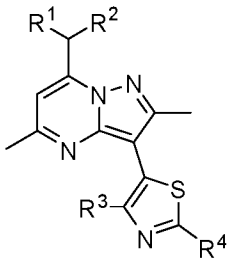
**[0216]** In an aspect provided herein, is a method of decreasing or reducing 17α-hydroxyprogesterone (17-OHP) levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):



, or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 60% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 70% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 80% of the subjects demonstrate reduction in 17-OHP. In embodiments, at least about 30% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 40% of subjects were in the standard

or normal range of 1200 ng/dL after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 60% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 60% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment.

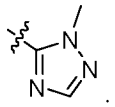
**[0217]** In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

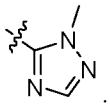


, or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 60% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 70% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 80% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 90% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least 100% of the subjects demonstrate reduction in androstenedione. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least 60% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range for androstenedione after treatment.

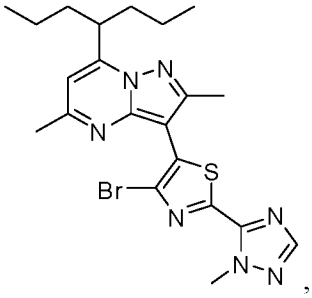
**[0218]** In certain embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl.

**[0219]** In certain embodiments, $R^3$ is Cl, Br, or methyl.

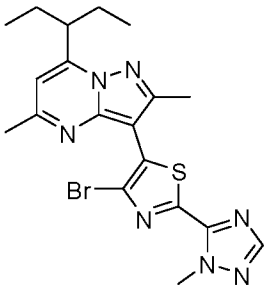
**[0220]** In certain embodiments, $R^4$ is Br, $R^aR^bN$–, pyridin-4-yl, morpholin-4-yl, or .

**[0221]** In certain embodiments, $R^4$ is morpholin-4-yl or .

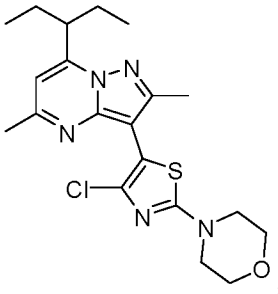
**[0222]** In certain embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$– and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

**[0223]** In certain embodiments, the compound is , or a pharmaceutically acceptable salt thereof.

**[0224]** In certain embodiments, the compound is

, or a pharmaceutically acceptable salt thereof.

**[0225]** In certain embodiments, the compound is

, or a pharmaceutically acceptable salt thereof.

**[0226]** In certain embodiments, a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is cyclically administered to a patient. Cycling therapy involves the administration of an active agent or a combination of active agents for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or

more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

**[0227]** In certain embodiments, in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein (e.g., treatment or prevention of testicular adrenal rest tumors (TART) or treatment or prevention of ovarian adrenal rest tumors (OART)), an appropriate dosage level of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof generally is ranging from about 1 mg to 3000 mg, from about 1 mg to 2000 mg, from about 1 mg to 1000 mg, from about 1 mg to about 500 mg, from about 5 mg to about 500 mg, from about 5 mg to about 400 mg, from about 5 mg to about 300 mg, from about 5 mg to about 250 mg, from about 5 mg to about 200 mg, from about 50 mg to about 200 mg, from about 10 mg to about 400 mg, from about 5 mg to about 25 mg, from about 10 mg to about 25 mg, or from about 25 to about 200 mg, which can be administered in single or multiple doses. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about

155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg/day.

**[0228]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is

administered in an amount of about 230 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or

prodrug thereof is administered in an amount of about 390 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg.

**[0229]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, or about 1000 mg.

**[0230]** For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing from about 1.0 mg to about 1,000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60

mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof for the symptomatic adjustment of the dosage to the patient to be treated. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 50 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 200 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate,

hydrate, or prodrug thereof.The pharmaceutical compositions can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg,

about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg,

about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered three times per day.

**[0231]** In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of one day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of two days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of three days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of four days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of five days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of six days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of seven days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of eight days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of nine days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of ten days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 11 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 12 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 13 days. In some embodiments, the compound of Formula (I), or an isotopic variant

thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 14 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 15 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 16 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 17 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 18 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 19 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 20 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 21 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 22 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 23 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 24 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 25 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 26 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 27 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 28 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 29 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 30 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 31 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 32 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 33 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 34 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 35 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 36 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 37 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 38 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 39 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 40 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 41 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 42 days or more.

**[0232]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate,

hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days.

**[0233]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 270 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I),

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 14 days.

**[0234]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is

administered in an amount of about 25 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the

compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is

administered in an amount of about 450 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 14 days.

**[0235]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 28 days. In certain

embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug

thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 28 days. In certain

embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 28 days.

**[0236]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt,

solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 28

days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt,

solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 28 days.

**[0237]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 255 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least

about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least

about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 42 days.

**[0238]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily

for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 42 days.

**[0239]** In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, or about 800 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered at least once per day.

**[0240]** In certain embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

**[0241]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

**[0242]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

**[0243]** In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

**[0244]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a

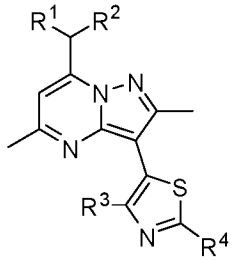
dose of from about 10 mg/day to about 400 mg/day is administered to the subject.In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day.

**[0245]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

**[0246]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 6 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 5 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 3 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 1 hour before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

**[0247]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

**[0248]** In another aspect is provided a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I): and a pharmaceutically acceptable excipientcomprising with a compound as described herein, including embodiments, or the structural Formulae (I) and a pharmaceutically acceptable excipient:



, or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$, and $R^4$ are as described herein, including embodiments.

**[0249]** In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0250]** In certain embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0251]** In certain embodiments, the pharmaceutical composition is administered orally.

**[0252]** In certain embodiments, the pharmaceutical composition is formulated as a capsule or tablet. In certain embodiments, the capsule or tablet comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360

mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 50 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 200 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0253]** In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

**[0254]** In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

**[0255]** In certain embodiments, the pharmaceutical composition is administered in the fed state. In certain embodiments, the pharmaceutical composition is administered in the fasted state. In certain embodiments, the pharmaceutical composition is administered at least once per day.

**[0256]** In certain embodiments, the pharmaceutical composition is administered at bedtime. In certain embodiments, the pharmaceutical composition is administered less than about 6 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 5 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 3 hours before sleep. In certain embodiments, the

pharmaceutical composition is administered less than about 2 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 1 hour before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep.

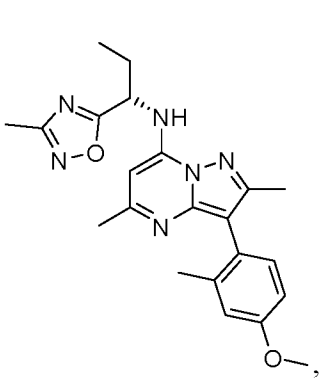
**[0257]** In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

**[0258]** In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

**[0259]** In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

**[0260]** In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

**[0261]** In certain embodiments, the the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In certain embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In certain embodiments, the mineralocorticoid is fludrocortisone. In certain embodiments, the additional chemotherapeutic agent is another $CRF_1$ antagonist. In certain embodiments, the $CRF_1$ antagonist is: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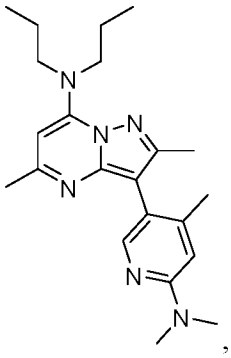
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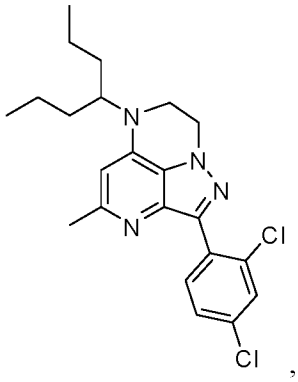
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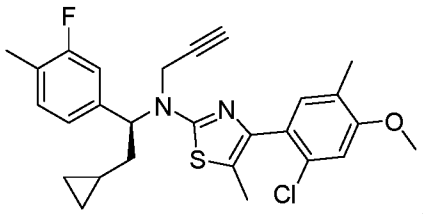
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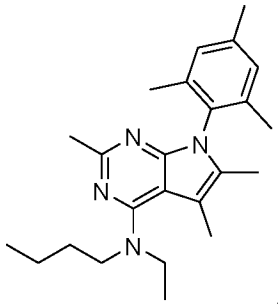
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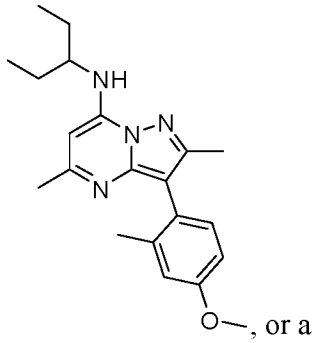
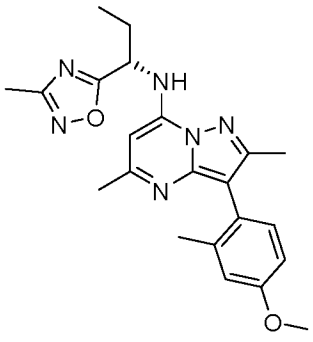

, or a

pharmaceutically acceptable salt thereof. In certain embodiments, the $CRF_1$ antagonist is



, or a pharmaceutically acceptable salt thereof.

**[0262]** In certain embodiments of the methods disclosed herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In certain embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0263]** In certain embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the radiation therapy is prior to administration of the $CRF_1$ antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0264]** In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. In some embodiments, a tablet comprises a solid carrier or an adjuvant. Liquid

pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil, or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. In some embodiments, a capsule comprises a solid carrier such as gelatin.

**[0265]** In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer's injection, or Lactated Ringer's injection. In some embodiments, preservatives, stabilisers, buffers, antioxidants, and/or other additives are included as required.

**[0266]** In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

**[0267]** The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, 2nd Edition, Rathbone *et al.*, Eds., Marcel Dekker, Inc.: New York, NY, 2008).

**[0268]** The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

**[0269]** The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

**[0270]** In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

**[0271]** The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

**[0272]** Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline

cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

**[0273]** Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

**[0274]** Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

**[0275]** Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

**[0276]** Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not

limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

**[0277]** It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

**[0278]** The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film

coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

**[0279]** The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

**[0280]** The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

**[0281]** Coloring and flavoring agents can be used in all of the above dosage forms.

**[0282]** The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

**[0283]** The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

**[0284]** The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be

prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

**[0285]** The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

**[0286]** Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methy1-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

**[0287]** Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl-and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

**[0288]** When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungi static concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

**[0289]** In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

**[0290]** The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

**[0291]** The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

**[0292]** Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and metliacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

**[0293]** Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

## V. Examples

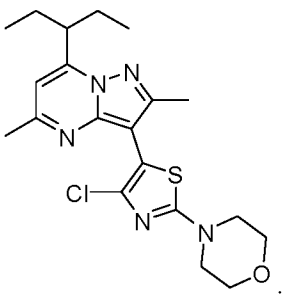
**[0294]** While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

**Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors**

**[0295]** Testicular adrenal rest tumors (TART) is a common complication in congenital adrenal hyperplasia (CAH) that is caused by adrenocorticotropin hormone (ACTH)–driven overstimulation of aberrant adrenal cells within the testes and results in impaired spermatogenesis and infertility. TARTS can be found anywhere on the testes, though a typical (very common) location is within the mediastinum. This is a particularly problematic location. Because of the central location of TARTs being in the mediastinum, compression of the nearby seminiferous tubules is common and can lead to obstructive azoospermia, irreversible damage to surrounding tissue, and permanent infertility in males.

**[0296]** Current treatment for TART consists of chronic high-dose glucocorticoids, a problematic therapy with significant side effects and a narrow therapeutic window. Given the serious nature of TART and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with TART. Compound 1, a high-affinity and selective small-molecule antagonist of the corticotropin-releasing factor type-1 ($CRF_1$) receptor, may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH (FIG. 12A-12B). Compound 1 has been shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. These promising results provide a rationale for investigating the use of Compound 1 in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.

**[0297]** The structure of Compound 1 is:



**[0298]** Building upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2 proof-of-concept study of Compound 1 in subjects with CAH, this Phase 2 will study Compound 1 specifically in male CAH subjects with TART for the first time. A sample size of approximately 12 subjects was selected to provide sufficient data for an initial evaluation of efficacy and safety in subjects with TART while maintaining feasible subject recruitment goals for this rare condition. Given the rarity of the disease and thus the small sample size that can be recruited, this study will be open label, and all enrolled subjects will receive active study drug. Subjects will serve as their own controls in that their outcome measures after 12 weeks of study drug dosing will be compared to their baseline measures.

**[0299]** The schedule of study visits (every 2 weeks through Week 4, then every 4 weeks for the remainder of the study) provides an appropriate balance between minimizing subject burden and closely monitoring subject safety and response to therapy. The 4-week post-treatment washout period will allow for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

**[0300]** The specification of study drug dosing at 10pm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers. The plasma $C_{max}$ (maximum concentration) for Compound 1 in the Phase 1 studies occurred approximately 5 hours after dosing. Therefore, Compound 1 will be dosed daily at 10pm in this study in order to achieve peak plasma study drug concentration at the time of day when most adrenal androgens are produced. Subjects will consume a standardized snack before taking study drug because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety. (**FIGS. 1A-1B**).

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the efficacy of Compound 1 in subjects with TART | • Reduction in the size/volume of TART on testicular ultrasound from screening to Week 12 |
| **Secondary** | |
| • To evaluate the safety of Compound 1 in subjects with TART | • Adverse events (AEs), serious adverse events (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs)<br>• Physical examination findings<br>• Vital signs<br>• Changes in electrocardiogram (ECG)<br>• Changes in clinical laboratory values |
| • To assess the pharmacodynamic (PD) biomarker effects of Compound 1 | • Changes in plasma concentrations of key PD biomarkers, including ACTH, 17-OHP, testosterone, androstenedione, luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone–binding globulin (SHBG), renin, and aldosterone from baseline to Week 12 |
| • To assess changes on semen analysis | • Changes in sperm count, morphology, and motility from baseline to Week 12 |
| • To assess changes in metabolism | • Changes in metabolic parameters, including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12<br>• Changes in body weight, body mass index (BMI), waist circumference, and blood pressure |
| • To evaluate changes in quality of life (QoL) and mood | • Changes in QoL measured using the Short Form 36 (SF-36)<br>• Changes in mood measured using the Hospital Anxiety and Depression Scale (HADS) |

**Study Population**

**[0301]** Approximately 12 male subjects with TART will be enrolled at approximately 6 investigative sites in the United States, United Kingdom, and possibly other countries. Up to 12 additional subjects may be added to further evaluate specific safety, PD, or efficacy findings.

**Eligibility Criteria**

Inclusion Criteria

- Adult male subjects aged 18 to 30, inclusive
- Documented historical diagnosis of CAH based on documented genetic mutation or historical documentation of elevated 17-OHP
- Diagnosis of TART via testicular ultrasound and/or magnetic resonance imaging (MRI) at screening with ≥1 lesion(s) measuring ≥2 cm in diameter
- On a stable regimen of GC replacement for ≥30 days before baseline
- Agree to follow contraception guidelines and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug
- Subject is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Exclusion Criteria

- Any clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
  - A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
  - Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m$^2$
  - Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
  - Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
- Any clinically significant psychiatric disorders, including any current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months
- HADS score >12 for either depression or anxiety
- At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at screening and baseline (eg,

C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)

- Clinically significant and abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:
  - Clinically meaningful abnormal ECG results, in the opinion of the Investigator
  - Fridericia-corrected QT interval (QTcF) >450 msec
  - Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
  - Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- A history that includes bilateral adrenalectomy or hypopituitarism
- Use of any other investigational drug within 30 days or 5 half-lives, whichever is longer, before initial screening
- Require use of prohibited concomitant medications, including strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids, hydrocortisone, and dexamethasone) within 30 days or 5 half-lives (whichever is longer) of first dose of study drug. Medications that are sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
- Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

**Study Duration**

**[0302]** The expected duration of study participation for each subject is up to approximately 20 weeks. This includes a screening period of ≤4 weeks, a treatment period of 12 weeks, and a safety follow-up period of 4 weeks.

**Study Design**

**[0303]** This is a Phase 2, open-label efficacy and safety study of Compound 1 for the treatment of TART. All subjects will receive a daily oral dose of Compound 1 for 12 weeks.In-clinic study visits will occur for screening and at Day 1 (baseline) and Weeks 2, 4, 8, 12 (end of treatment), and 16 (follow-up).

**Dose, Route, Regimen**

**[0304]** All subjects will receive a daily oral dose of Compound 1 for 12 weeks. Subjects will receive 600 mg/day during the first 2 weeks and 1000 mg/day during the remaining 10 weeks of the treatment period. Study drug will be taken daily at 10pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

**[0305]** On mornings of study visits with 8am blood draws for laboratory assessments, subjects should take their morning glucocorticoid replacement after the blood draws. For all other days during the study, subjects may take their morning glucocorticoid replacement at their usual time (generally between 6am and 8am).

**[0306]** If a subject experiences a Grade 3 or higher TEAE considered at least possibly related to study drug, the Investigator may reduce the subject's daily dose of Compound 1 down in increments of 200 mg. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria.

**Investigational Drug**

**[0307]** Compound 1 is a small-molecule $CRF_1$ receptor antagonist and will be supplied as 200-mg, size 1, white, hard gelatin capsules.

**Example 2.**

**[0308]** Since elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1, a small-molecule antagonist of the $CRF_1$ receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. 12A-12B). The safety profile of Compound 1 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH is currently ongoing.

*Nonclinical Toxicology of Compound 1*

**[0309]** The nonclinical safety profile of Compound 1 has been evaluated in repeat-dose range-finding and definitive toxicology studies of up to 91 days in duration in rats and dogs using the clinically relevant route (oral) and schedule of administration (once daily). In rats and beagle dogs administered oral Compound 1 once daily for 91 consecutive days at doses up to 2000 mg/kg/day, toxicologic findings were all mild and limited to the male reproductive tract, and all Compound 1-related findings were reversible following a 6-week treatment-free recovery period.

**[0310]** Additionally, a fertility toxicology study was conducted in rats. In this study, male rats were administered oral Compound 1 once daily at 0, 5, 20, or 1000 mg/kg for 85 to 87 days (70 days before mating, during mating, and ≤4 days between mating and necropsy). Male reproductive performance (mean day of mating, mating and fertility indices, and conception rates) was unaffected by Compound 1 treatment. Untreated females mated with the Compound 1-treated males had no ovarian and uterine effects.

**[0311]** In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay have also been conducted.

*Clinical Experience with Compound 1*

**[0312]** To date, a total of 53 subjects, all healthy adults aged 21 to 65 years, have been treated with at least 1 dose of Compound 1 in 2 Phase 1 studies. The first-in-human study of Compound 1 (Study I3C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study I3C-FW-BLAB) evaluated repeat doses of 50 mg, 100 mg, or 200 mg Compound 1 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs). Compound 1 has been well tolerated in healthy human subjects, with no SAEs, AEs leading to discontinuation, or dose-limiting toxicities (DLTs). A maximum tolerated dose has not been reached in humans.

**[0313]** An ongoing Phase 2 open-label study (Study Compound 2) is currently evaluating the safety and efficacy of Compound 1 dosed once daily for 6 weeks in adults with classic CAH. In the initial Cohort A of this study, all subjects are dosed starting at 200 mg/day for 14 days, escalating for each subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLTs at the previous dose level. (**FIGS. 2-3**).

*Known Potential Risks*

**[0314]** Because the reversible testicular effects (degeneration/atrophy) observed in rats and dogs treated with high-dose Compound 1 (2,000 mg/kg/day) are likely associated with on-target (mechanism-driven) effects, these effects are likely to be relevant to human risk. However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical laboratory markers of testicular function (LH and FSH) when Compound 1 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Clinical laboratory measures

of testicular function (LH, FSH, inhibin B, and SHBG) will be assessed throughout this study to monitor the risk of testicular injury. Testicular ultrasounds and semen analysis will also be performed at screening/baseline and the end of the treatment period.

**[0315]** Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the Phase 1 clinical studies. Clinical laboratory measures of liver chemistry will be assessed throughout this study, and strict individual treatment stopping criteria for liver chemistry findings are in place.

**[0316]** Compound 1-induced effects on the thyroid gland were noted in dogs after 91 days of high-dose (2,000 mg/kg/day) treatment but not in any other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) were not evaluated in the Phase 1 studies but will be monitored throughout this study.

*Known Potential Benefits*

**[0317]** Early clinical studies suggests that Compound 1 is effective as a $CRF_1$ receptor antagonist, a mechanism of action that supports the clinical investigation of Compound 1 for treatment of TART. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. 12A-12B).

*Assessment of Potential Risks and Benefits*

**[0318]** The mild and reversible toxicologic effects of Compound 1 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a $CRF_1$ receptor antagonist, Compound 1 is intended to reduce abnormally elevated ACTH levels, which in TART drives overstimulation of aberrant adrenal cells within the testes. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. In TART, where baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

**[0319]** Given the serious nature of TART and the limitations (and risks) of chronic steroid therapy, new treatment modalities are needed for patients with TART. Given the acceptable safety and tolerability profile of Compound 1 in healthy volunteers from the Phase 1 program, the low probability of demonstrating meaningful PD marker changes in healthy subjects, and the lack of any clear benefit to exposing more healthy subjects to study drug, the Sponsor believes the benefit-to-risk profile favors the entry of Compound 1 into Phase 2 in subjects with TART.

**Example 3. Congenital Andrenal Hyperplasia (CAH)**

**[0320]** CAH results from a genetic defect in the 21-hydroxylase enzyme. CAH patients are thus unable to produce cortisol. Without cortisol to provide negative feedback, patients over-produce ACTH. High ACTH promotes the overproduction of potent androgens (male sex hormones). Without wishing to be bound by theory, Compound 1 blocks $CRF_1$ receptor to prevent ACTH release by the pituitary and associated drive on the hypothalamic-pituitary-adrenal axis. Replacement of cortisol to physiological levels will correct cortisol deficiency, however, will not lower ACTH, resulting in hyperplasia of adrenal gland and associated overproduction of adrenal androgens.

**[0321]** As shown in **FIGS. 4** and **5A-5B**, the attenuation of ACTH demonstrates target engagement and functional $CRF_1$ receptor antagonism. 80% of subjects demonstrated reduction in ACTH. 70% of subjects demonstrated > 25% reduction in ACTH. 30% of subjects were in the normal range (*) after treatment with a $CRF_1$ receptor antagonist.

**[0322] FIGS. 6** and **7A-7B** demonstrate "control" of disease based on standard guidelines, which would then allow steroid taper. 80% of subjects demonstrated reduction in 17-OHP. 50% of subjects demonstrated > 25% reduction in ACTH. 50% of subjects were in the guideline range (*; 1200 ng/dL) after treatment with a $CRF_1$ receptor antagonist.

**[0323] FIGS. 8** and **9A-9B** demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess androgen production and associated symptoms. 100% of subjects demonstrated reduction in androstenedione (at various doses). 60% of subjects demonstrated > 25% reduction in androstenedione. 50% of subjects were within the normal reference range after treatment with a $CRF_1$ receptor antagonist.

**[0324] FIGS. 10A-10B** show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a $CRF_1$ receptor antagonist.

**[0325] FIGS. 11A-11B** demonstrate Compound 1 is a potent, selective, and functional $CRF_1$ receptor antagonist. In in vitro and ex vivo studies, Compound 1 was determined to be a potent and selective $CRF_1$ receptor antagonist with high affinity and selective for the $hCRF_1$ receptor. Compound 1 was found to have functional potency to inhibit adenylate cyclase activity ($CRF_1$ receptor-mediated downstream cascade), demonstrating in vitro efficacy as a $CRF_1$ receptor antagonist. Compound 1 was found to significantly inhibit CRF-induced locomotor behavior in response to i.c.v. administration of CRF (**FIG. 11B**).

**[0326] FIGS. 12A-12B** demonstrate single pill of $CRF_1$ receptor antagonist (i.e., as described in US 2017/0020877 A1) improves ACTH and 17-OHP in CAH patients.

**[0327] FIG. 13** shows the subject level hormone changes (ACTH, 17-OHP, and androstenedione) by dose of a $CRF_1$ receptor antagonist.

**Example 4. Assess reduction in excess ACTH and adrenal steroid production**

**[0328]** The objectives of the study are: to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable gluococorticoid regimen; to evaluate the safety and tolerability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

**ELIGIBILITY CRITERIA**

**[0329]** Inclusion Criteria:

- Adult males and females 18 years or older
- Diagnosis of classic CAH due to 21-hydroxylase deficiency
- Morning 17OHP ≥800 ng/dL, before taking any morning GC dose
- On a stable regimen of gluococorticoid replacement for ≥30 days before enrollment

**[0330]** Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease within 30 days of screening
- Clinically significant psychiatric disorder
- History of bilateral adrenalectomy or hypopituitarism

**STUDY DESIGN**

**[0331] FIG. 14** depicts the proof of concept and escalating QD dosing at 10 PM for Cohort A and the single dose level and BID dosing at 10 AM and 10 pm for Cohort B.

**BASELINE CHARACTERISTICS**

**[0332]** Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 partcipants were enrolled and received at least 1 dose of Compound 1. One participant withdrew early because of an occupation-related scheduling conflict. In Cohort B, 9 participants were enrolled and received at least one dose of Compound 1. One participant was withdrawn upon discovery of a major protocol violation at Baseline and did not have postbaseline efficacy/PK data. Thus, baseline characteristics are calculated for n=8 in Cohort B. One participant in Cohort B was taking both HC and prednisone.

*Table 1 – Baseline characteristics of each cohort*

| Parameter | Cohort A (n=10) | Cohort B (n=8) |
|---|---|---|
| Demographics | | |
| Age (years), mean (range) | 39.3 (24-66) | 36.8 (19-66) |
| Sex | 5M, 5F | 1M, 7F |
| Bmi ($kg/m^2$), mean ± SD | 31.5 ± 12.0 | 31.1 ± 6.7 |

| | | |
|---|---|---|
| Daily GC dose (mg HC equivalents), mean range<br>Types of GCs | 28 (13-40)<br>4 JC, 3 pred, 3 dex | 35 (20-50)<br>2HC, 4 pred, 3 dex |
| 17OHP at screening[a] (ng/dl), mean ± SD | 5,985 ± 6,347 | 4,592 ±4,624 |

Abbreviations: 17OHP: 17-hydroxyprogesterone; BMI: body mass index; dex: dexamethasone; F: female; GC: glucocorticoid; HC: hydrocortisone; M: male; pred: prednisone; SD: standard deviation.
a 17OHP reference ranges: 27-199 ng/dL males, 15-290 ng/dL females.

**SAFETY**

**[0333]** Across both cohorts, Compound 1 was generally well tolerated. The most common type of adverse event (AE) was gastrointestinal disorders There were no serious AEs and no AEs leading to withdrawal.

**PHARMACOKINETICS**

**[0334]** Over a wide range of doses (200 to 1000 mg QD), Compound 1exhibited a predictable, dose-dependent PK profile.

**EFFICACY**

**[0335] FIG. 15A-15D** show the changes in levels of Androstenedione (A4) across both cohorts. Levels of A4 improved at ≥1 dose level for 10 out of 10 participants in Cohort A and 6 out of 8 participants in Cohort B. Excess A4 is associated with clinical sequelae in CAH. Attenuation of A4 demonstrates control of adrenal androgen.

**[0336] FIG. 16A-16D** show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 6 out of 7 participants in Cohort B. 17OHP is a critical hormone in CAH diagnosis and management. Attenuation of 17OHP demonstrates control of adrenal steroid production.

**[0337] FIG. 17A-17D** show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 5 out of 7 participants in Cohort B. Attenuation of ACTH demonstrates target engagement and fucntional $CRF_1$ receptor antagonism.

*Table 2 – Percentage change from baseline in ACTH, 17OHP and A4.*

| | Cohort A | | | Cohort B |
|---|---|---|---|---|
| | 200 mg QD (Week 2) | 600 mg QD (Week 4) | 1000 mg QD (Week 6) | 200 mg BID (Week 2) |
| ACTH | -25.7 (±51.6) | -60.1 (±37.5) | -32.7 (±47.0) | -36.5 (±58.0) |
| 17OHP | +22.2 (±172.3) | -23.7 (±64.2) | -13.8 (±74.7) | -47.8 (±63.3) |
| A4 | -12.1 (±47.4) | -33.2 (±36.5) | -28.6 (±44.6) | -16.0 (±81.4) |

**CONCLUSIONS**

**[0338]** Compound 1, a potent and selective $CRF_1$ receptor antagonist, offers a novel nonsteroidal oral treatment approach for CAH. Compound 1 was well tolerated and efficacious in reducing excess ACTH, 17OHP, and androstenedione in patients with classic CAH.

Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

**[0339]** While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

# METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## CROSS-REFERENCE

**[0001]** This application is a continuation of U.S. Application No. 18/941,832, filed November 8, 2024, which is a continuation of U.S. Application No. 17/667,285, filed on February 8, 2022, which is a continuation of U.S. Application No. 17/081,694 filed on October 27, 2020, which issued as U.S. Pat. No. 11,304,950 on April 19, 2022, and which is a continuation of International Application No. PCT/US2019/029486 filed on April 26, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed April 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019, each of which is entirely incorporated herein by reference.

## BACKGROUND

**[0002]** Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

**[0003]** CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

**[0004]** Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, *inter alia*, are solutions to these and other problems in the art.

## SUMMARY

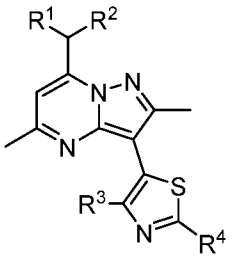
**[0005]** Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

**[0006]** Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

**[0007]** One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

**[0008]** In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

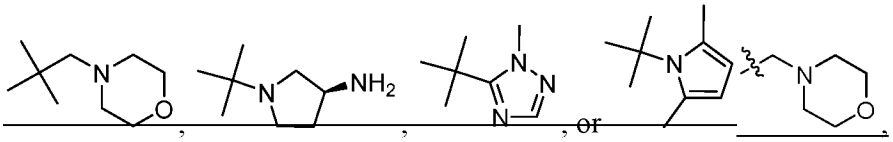
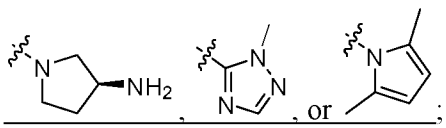
**[0009]** One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):


(I), or a pharmaceutically acceptable salt thereof,

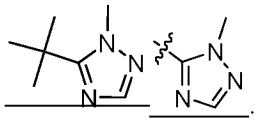
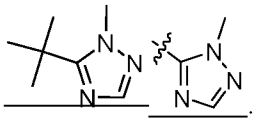
wherein:

$R^1$ and $R^2$ are independently ethyl or n-propyl;

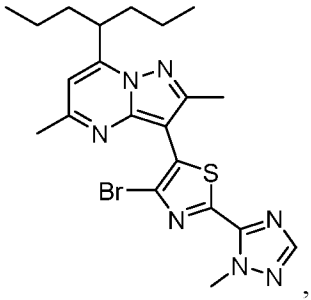
$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

$R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , or ;

$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

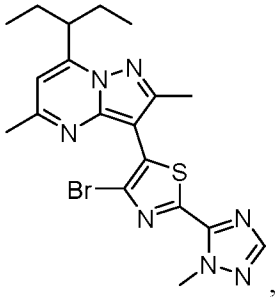
**[0010]** In some embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl. In some embodiments, $R^3$ is Cl, Br, or methyl. In some embodiments, $R^4$ is Br, $R^aR^bN$–, pyridin-4-yl, morpholin-4-yl, or . In some embodiments, $R^4$ is morpholin-4-yl or .

**[0011]** In some embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$– and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl. In some embodiments, the compound is



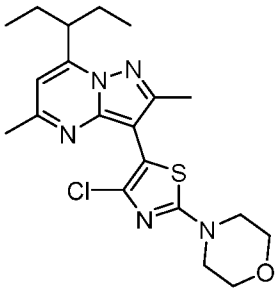
, or a pharmaceutically acceptable salt thereof.

**[0012]** In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

**[0013]** In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

**[0014]** In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

**[0015]** In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a

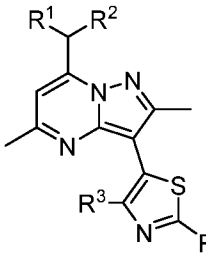
pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

**[0016]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

**[0017]** In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

**[0018]** In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

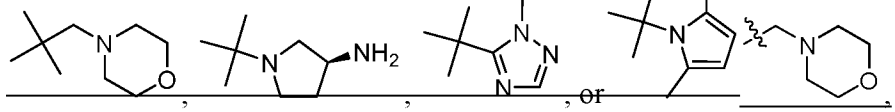
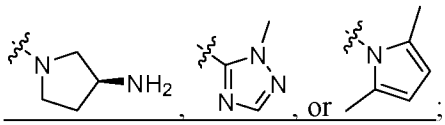
**[0019]** One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:


(I), or a pharmaceutically acceptable salt thereof,

wherein:

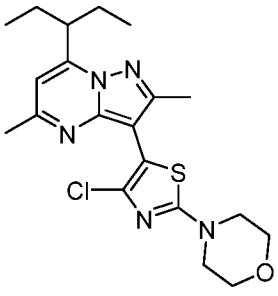
$R^1$ and $R^2$ are independently ethyl or n-propyl;

$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

$R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , or ;

$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

**[0020]** In some embodiments, the compound of Formula (I) has the structure:


, or a pharmaceutically acceptable salt thereof.

**[0021]** In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0022]** In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

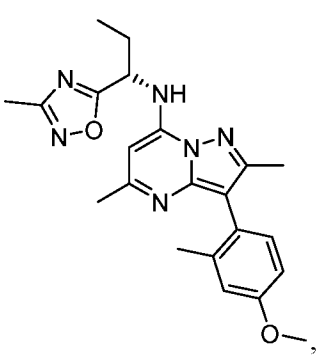
**[0023]** In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

**[0024]** In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

**[0025]** In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

**[0026]** In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

**[0027]** In some embodiments, the additional chemotherapeutic agent is another $CRF_1$ antagonist. In some embodiments, the $CRF_1$ antagonist is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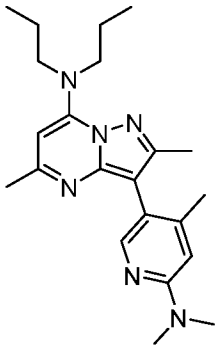
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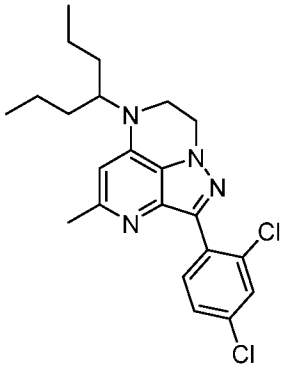
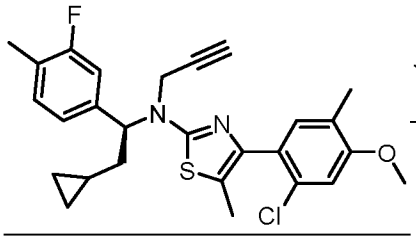
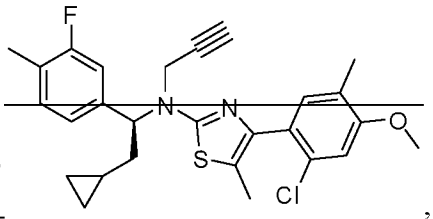

, SSR-126374,


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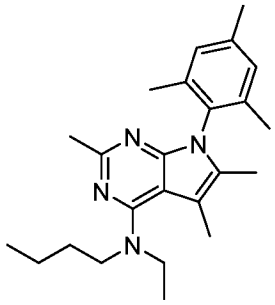
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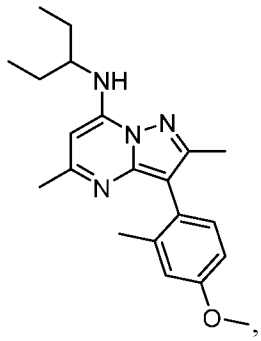
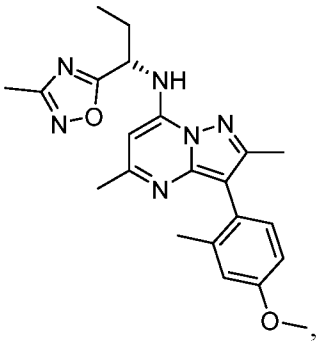

, or a pharmaceutically acceptable salt thereof.

**[0028]** In some embodiments, the $CRF_1$ antagonist is


, or a pharmaceutically acceptable salt thereof.

**[0029]** In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

**[0030]** In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural

Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

**[0031]** In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0032]** In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the $CRF_1$ antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0033]** In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0034]** Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

## INCORPORATION BY REFERENCE

**[0035]** All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0036]** The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

**[0037] FIG. 1A-1B**. A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics **(A).** A schematic representation of inhibition of $CRF_1$ with a $CRF_1$ antagonist (Compound 1) **(B)**.

**[0038] FIG. 2**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a $CRF_1$ antagonist (Compound 1).

**[0039] FIG. 3**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a $CRF_1$ antagonist (Compound 1).

**[0040] FIG. 4**. Graphic representation of patient-level response (measuring ACTH levels) to a $CRF_1$ antagonist (Compound 1).

**[0041] FIG. 5A-5B**. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a $CRF_1$ antagonist [~~Subject 003001~~Patient 10 **(A)**; ~~Subject 007002~~ Patient 8 **(B)**].

**[0042] FIG. 6**. Graphic representation of patient-level response (measuring 17-OHP levels) to a $CRF_1$ antagonist (Compound 1).

**[0043] FIG. 7A-7B**. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to a $CRF_1$ antagonist [~~Subject 003001~~Patient 10 **(A)**; ~~Subject 007002~~ Patient 8 **(B)**].

**[0044] FIG. 8**. Graphic representation of patient-level response (measuring androstenedione levels) to a $CRF_1$ antagonist (Compound 1).

**[0045] FIG. 9A-9B**. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a $CRF_1$ antagonist (Compound 1) [~~Subject 003001~~Patient 10 **(A)**; ~~Subject 007002~~ Patient 8 **(B)**].

**[0046] FIG. 10A-10B**. Images of a patient with TART pre-treatment with a $CRF_1$ antagonist (Compound 1) **(A)** and 6-weeks post-treatment with a $CRF_1$ antagonist (Compound 1) **(B)**.

**[0047] FIG. 11A-11B**. Graphic representation of an *in vitro* binding assay of a $CRF_1$ antagonist (Compound 1); $^{125}$I-sauvagine binding to rat cerebellar membranes one hour after oral

administration of increasing Compound 1 doses **(A)** and *in vivo* inhibition of CRF-induced activity after treatment with a $CRF_1$ antagonist; Compound 1 (oral, 10 mg/kg) **(B)**.

**[0048] FIG. 12A-12B**. ~~Graphic representation of ACTH levels **(A)** and 17-OHP levels **(B)** after treatment with a $CRF_1$ antagonist (Compound 1)~~ Graphic representation of ACTH levels (A) and 17-OHP levels (B) after treatment with a $CRF_1$ antagonist.

**[0049] FIG. 13**. Graphic representation of hormone responses after treatment with a $CRF_1$ antagonist (Compound 1).

**[0050] FIG. 14** depicts the proof of concept and escalating QD dosing at 10 pm for Cohort A and the single dose level and BID dosing at 10 am and 10 pm for Cohort B.

**[0051] FIG. 15A-15D** are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

**[0052] FIG. 16A-16D** are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

**[0053] FIG. 17A-17D** are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

## DETAILED DESCRIPTION

**[0054]** While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

### I. Definitions

**[0055]** The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

**[0056]** Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

**[0057]** The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., $C_1$-$C_{10}$ means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl,

isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

**[0058]** The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -$CH_2CH_2CH_2CH_2$-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

**[0059]** The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: -$CH_2$-$CH_2$-O-$CH_3$, -$CH_2$-$CH_2$-NH-$CH_3$, -$CH_2$-$CH_2$-N($CH_3$)-$CH_3$, -$CH_2$-S-$CH_2$-$CH_3$, -$CH_2$-$CH_2$, -S(O)-$CH_3$, -$CH_2$-$CH_2$-S(O)$_2$-$CH_3$, -CH=CH-O-$CH_3$, -Si($CH_3$)$_3$, -$CH_2$-CH=N-O$CH_3$, -CH=CH-N($CH_3$)-$CH_3$, -O-$CH_3$, -O-$CH_2$-$CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -$CH_2$-NH-O$CH_3$ and -$CH_2$-O-Si($CH_3$)$_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

**[0060]** Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -$CH_2$-$CH_2$-S-$CH_2$-$CH_2$- and -$CH_2$-S-$CH_2$-$CH_2$-NH-$CH_2$-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and

heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

**[0061]** The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

**[0062]** The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo($C_1$-$C_4$)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

**[0063]** The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

**[0064]** The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term

"heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

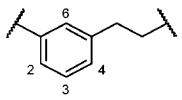
**[0065]** Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted

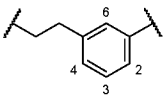
heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

**[0066]** The symbol "〰" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

**[0067]** The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

**[0068]** The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



or


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**[0069]** An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -CHO, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2CH_3$ $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $–NHNH_2$, $–ONH_2$, $–NHC(O)NHNH_2$, substituted or unsubstituted $C_1$-$C_5$ alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

**[0070]** Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

**[0071]** Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', $-NR"C(O)_2R'$, -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, –NR'NR"R"', –ONR'R", –NR'C(O)NR"NR"'R"", -CN, $-NO_2$, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R"', and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g.,

aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

**[0072]** Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, -SiR'R"R'", -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", $-NR"C(O)_2R'$, -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'", $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, –NR'NR"R'", –ONR'R", –NR'C(O)NR"NR'"R"", -CN, $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro($C_1$-$C_4$)alkoxy, and fluoro($C_1$-$C_4$)alkyl, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R'", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" groups when more than one of these groups is present.

**[0073]** Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent),

the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

**[0074]** Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

**[0075]** Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C"R"R"')_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R", and R"' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

**[0076]** As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

**[0077]** A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -$CF_3$, -CN, -OH, -$NH_2$, -COOH, -$CONH_2$, -$NO_2$, -SH, -$SO_3H$, -$SO_4H$, -$SO_2NH_2$, –$NHNH_2$, –$ONH_2$, –NHC=(O)$NHNH_2$, –NHC=(O) $NH_2$, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -$OCF_3$, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, -$CF_3$, -CN, -OH, -$NH_2$, -COOH, -$CONH_2$, -$NO_2$, -SH, -$SO_3H$, -$SO_4H$, -$SO_2NH_2$, –$NHNH_2$, –$ONH_2$, –NHC=(O)$NHNH_2$, –NHC=(O) $NH_2$, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -$OCF_3$, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, -$CF_3$, -CN, -OH, -$NH_2$, -COOH, -$CONH_2$, -$NO_2$, -SH, -$SO_3H$, -$SO_4H$, -$SO_2NH_2$, –$NHNH_2$, –$ONH_2$, –NHC=(O)$NHNH_2$, –NHC=(O) $NH_2$, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -$OCF_3$, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, -$CF_3$, -CN, -OH, -$NH_2$, -COOH, -$CONH_2$, -$NO_2$, -SH, -$SO_3H$, -$SO_4H$, -$SO_2NH_2$, –$NHNH_2$, –$ONH_2$, –NHC=(O)$NHNH_2$, –NHC=(O) $NH_2$, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -$OCF_3$, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

**[0078]** A "size-limited substituent" or " size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_{20}$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_8$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or

unsubstituted $C_6$-$C_{10}$ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

**[0079]** A "lower substituent" or " lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_8$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

**[0080]** In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

**[0081]** In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted $C_1$-$C_{20}$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_8$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted $C_1$-$C_{20}$ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted $C_3$-$C_8$ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted $C_6$-$C_{10}$ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

**[0082]** In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_8$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted $C_1$-$C_8$ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted $C_3$-$C_7$ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted $C_6$-$C_{10}$ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

**[0083]** Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

**[0084]** As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

**[0085]** The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

**[0086]** It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

**[0087]** Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

**[0088]** Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by $^{13}C$- or $^{14}C$-enriched carbon are within the scope of this invention.

**[0089]** The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium ($^{3}H$), iodine-125 ($^{125}I$), or carbon-14 ($^{14}C$). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

**[0090]** It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

**[0091]** "Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

**[0092]** The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted $C_1$-$C_{20}$ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted $C_1$-$C_{20}$ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

**[0093]** Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple $R^{13}$ substituents are present, each $R^{13}$ substituent may be distinguished as $R^{13A}$, $R^{13B}$, $R^{13C}$, $R^{13D}$, etc., wherein each of $R^{13A}$, $R^{13B}$, $R^{13C}$, $R^{13D}$, etc. is defined within the scope of the definition of $R^{13}$ and optionally differently.

**[0094]** A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

**[0095]** Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

**[0096]** The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities,

acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

**[0097]** Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

**[0098]** The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

**[0099]** In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after

administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

**[0100]** Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

**[0101]** "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of a compound to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

**[0102]** The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

**[0103]** A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

**[0104]** The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally

occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and "protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

**[0105]** A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, *e.g.*, in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

**[0106]** "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

**[0107]** The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

**[0108]** As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

**[0109]** The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in

comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist. In embodiments, an agonist is a molecule that interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

**[0110]** As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

**[0111]** The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

**[0112]** The terms "corticotropin-releasing factor type-1," "$CRF_1$," "corticotropin-releasing hormone receptor 1," and "CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms

include any recombinant or naturally-occurring form of $CRF_1$ variants thereof that maintain $CRF_1$ activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of $CRF_1$ variants (e.g., frameshift mutations) thereof that maintain $CRF_1$ activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype $CRF_1$). In embodiments, the $CRF_1$ protein encoded by the *CRHR1* gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

**[0113]** The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.*).

**[0114]** The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

**[0115]** As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal

carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

**[0116]** The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

**[0117]** "Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

**[0118]** "Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

**[0119]** The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal

leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

**[0120]** The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

**[0121]** The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

**[0122]** The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, medullary thyroid carcinoma, familial medullary thyroid carcinoma,

acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

**[0123]** The terms “treating” or “treatment” refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term “treating” and conjugations thereof, may include

prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

**[0124]** "Treating" or "treatment" as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (*e.g.*, ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

**[0125]** "Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

**[0126]** The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

**[0127]** "Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

**[0128]** An "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see*, *e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a CRF1 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

**[0129]** For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

**[0130]** Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has

been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

**[0131]** The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

**[0132]** The terms "QD," "qd," and "q.d." refer to once a day, i.e., a drug or therapeutic agent is administered once a day for the duration of the therapeutic regimen.

**[0133]** The terms "BD," "bd," and "b.i.d." refer to twice a day, i.e., a drug or therapeutic agent is administered two times a day for the duration of the therapeutic regimen.

**[0134]** The terms "QID," "qid," and "q.i.d." refer to three times a day, i.e., a drug or therapeutic agent is administered three times a day for the duration of the therapeutic regimen.

**[0135]** Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

**[0136]** As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.,* a mini-osmotic pump, to a subject. Administration is by any route, including

parenteral and transmucosal (*e.g.,* buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.,* intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.,* by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the

present invention into the target cells in vivo. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

**[0137]** By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

**[0138]** For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

**[0139]** Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

**[0140]** The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

**[0141]** In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer

(e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

**[0142]** The compounds described herein can be administered to treat a fertility disease or disorder and/or cancer. In this regard, the compounds disclosed herein may be administered either alone to treat such diseases or disorders or may be co-administered with another therapeutic agent to treat such diseases or disorders.

**[0143]** The compounds disclosed herein may be co-administered with an agonist or antagonist of $CRF_1$ function. The compounds described herein can be co-administered with conventional anti-cancer/chemotherapeutic.

**[0144]** "Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (*e.g.,* cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (*e.g.,* 5- azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (*e.g.,* vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (*e.g.,* irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.,* doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g.,

daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine;

gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re

186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including

recombinant interleukin II, or rlL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198

(Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, lnanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, lsoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (*e.g.,* dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (*e.g.,* Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (*e.g.,* anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (*e.g.,* anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (*e.g.,* anti-CD20 monoclonal antibody conjugated to $^{111}$In, $^{90}$Y, or $^{131}$I, *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin,

vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa ™), erlotinib (Tarceva ™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

**[0145]** "Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

**[0146]** The compounds disclosed herein may be co-administered with an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5.alpha.-reductase such as finasteride; (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-

methoxy-6-(3-morpholinopropoxy)quinazoli- n-4-amine (gefitinib, AZD 1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazoli- n-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family; (v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin .alpha.v.beta.3 function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

**[0147]** In embodiments, the compounds disclosed herein can be co-administered with an antibody, such as a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax I1-15) or antibody modulating Ig function such as anti-IgE (for example omalizumab).

**[0148]** In embodiments, treatment of cancer includes administration of an effective amount of at least two of the following: a CRF1 inhibitor, an inhibitor of the PD-L1/PD-1 pathway, an inhibitor of CTLA-4, an agonistic antibody of CD137 (4-1BB). In some embodiments, the method may comprise the use of two or more combinations.

**[0149]** In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as $^{47}Sc$, $^{64}Cu$, $^{67}Cu$, $^{89}Sr$, $^{86}Y$, $^{87}Y$, $^{90}Y$, $^{105}Rh$, $^{111}Ag$, $^{111}In$, $^{117m}Sn$, $^{149}Pm$, $^{153}Sm$, $^{166}Ho$, $^{177}Lu$, $^{186}Re$, $^{188}Re$, $^{211}At$, and $^{212}Bi$, optionally conjugated to antibodies directed against tumor antigens.

**[0150]** In addition, a $CRF_1$ inhibitor may be combined with the therapeutic administration of immune cells, sometimes referred to as adoptive cell transfer. These cells may be cells from the patient, a genetically related or unrelated donor, they may be genetically modified (e.g. CAR-T cells, NK cells, etc), cell lines, genetically modified cell lines and live or dead versions of the above. CRF1 inhibitors may also be combined with vaccines of any kind (e.g. protein/peptide, viral, bacterial, cellular) to stimulate immune responses to cancer.

**[0151]** The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

**[0152]** The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

**[0153]** The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein may be administered once daily until study reached endpoint. The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein may be administered at least three times but in some studies four or more times depending on the length of the study and/or the design of the study.

**[0154]** The methods disclosed herein may be used in combination with additional cancer therapy. In some embodiments, the distinct cancer therapy comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy. In some embodiments, the cancer is a chemotherapy-resistant or radio-resistant cancer.

**[0155]** A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability

to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaroytic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (*e.g.*, spodoptera) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

**[0156]** "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

**[0157]** The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. In some embodiments, a CRF1 associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with $CRF_1$ (e.g. an endocrine disorder, a cancer including but not limited to TART or OART). A $CRF_1$ modulator is a compound that increases or decreases the activity or function or level of activity or level of function of $CRF_1$. A modulator may act alone, or it may use a cofactor, e.g., a protein, metal ion, or small molecule. Examples of modulators include small molecule compounds and other bioorganic molecules. Numerous libraries of small molecule compounds (e.g., combinatorial libraries) are commercially available and can serve as a starting point for identifying a modulator. The skilled artisan is able to develop one or more assays (e.g., biochemical or cell-based assays) in which such compound libraries can be screened in order to identify one or more compounds having the desired properties; thereafter, the skilled medicinal chemist is able to optimize such one or more compounds by, for example, synthesizing and evaluating analogs and derivatives thereof. Synthetic and/or molecular modeling studies can also be utilized in the identification of an activator.

**[0158]** The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms "modulate", "modulation" and the like refer to the ability of a molecule

(e.g., an activator or an inhibitor) to increase or decrease the function or activity of $CRF_1$, either directly or indirectly, relative to the absence of the molecule.

**[0159]** The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, an endocrine disorder, a disease associated with $CRF_1$ activity, a $CRF_1$ associated disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, an endocrine disorder associated with $CRF_1$ activity or function may be an endocrine disorder that results (entirely or partially) from aberrant $CRF_1$ function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or an endocrine disorder wherein a particular symptom of the disease is caused (entirely or partially) by aberrant $CRF_1$ activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, an endocrine disorder associated with $CRF_1$ activity or function or a $CRF_1$ associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., $CRF_1$ modulator, $CRF_1$ inhibitor, or $CRF_1$ antagonist), in the instance where increased $CRF_1$ activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART). For example, an endocrine disorder associated with $CRF_1$ activity or function or a $CRF_1$ associated endocrine disorder, may be treated with an $CRF_1$ modulator or $CRF_1$ inhibitor, in the instance where increased $CRF_1$ activity or function (e.g. signaling pathway activity) causes the disease.

**[0160]** The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

**[0161]** The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propogated to other signaling pathway components. For example, binding of a $CRF_1$ with a compound as described herein may reduce the level of a product of the $CRF_1$ catalyzed reaction or the level of a

downstream derivative of the product or binding may reduce the interactions between the $CRF_1$ or a reaction product and downstream effectors or signaling pathway components (e.g., MAP kinase pathway), resulting in changes in cell growth, proliferation, or survival.

**[0162]** As used herein, the terms "corticotropin-releasing factor type-1," "$CRF_1$," "corticotropin-releasing hormone receptor 1," and "CHHR1" and all other related art-accepted terms, many of which are set forth below, refer to a compound capable of modulating, either directly or indirectly, the $CRF_1$ receptor in an *in vitro* assay, an *in vivo* model, and/or other means indicative of therapeutic efficacy. The terms also refer to a compound that exhibits at least some therapeutic benefit in a human subject.

**[0163]** The phrase "in a sufficient amount to effect a change" means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject's feeling of well-being).

**[0164]** The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

**[0165]** "Substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

**[0166]** The terms "specifically binds" and "selectively binds," when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample. The antibody, or binding composition derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen, or a variant or mutein thereof, with an affinity that is at least two-fold greater, at least 10-times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antibody, or binding composition derived therefrom. In

embodiments, the antibody will have an affinity that is greater than about $10^9$ liters/mol, as determined by, e.g., Scatchard analysis (Munsen, et al. (1980) Analyt. Biochem. 107:220-239).

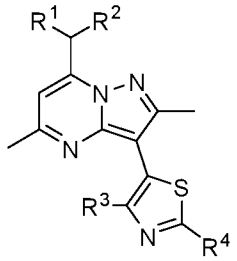
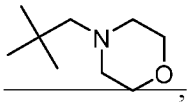
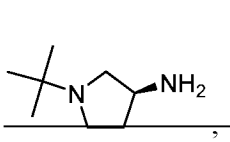
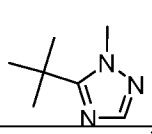
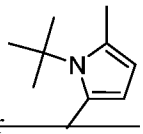
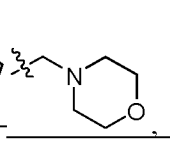
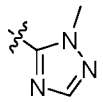
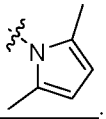
**[0167]** The terms "DNA," "nucleic acid," "nucleic acid molecule," "polynucleotide" and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, messenger RNA (mRNA), complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

**[0168]** As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced (e.g., muteins); for example, the change is generated in the laboratory by human intervention ("hand of man"). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

**[0169]** The term "muteins" as used herein refers broadly to mutated recombinant proteins. These proteins usually carry single or multiple amino acid substitutions and are frequently derived from cloned genes that have been subjected to site-directed or random mutagenesis, or from completely synthetic genes.

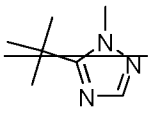
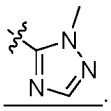
## II. Compounds

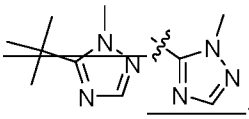
**[0170]** In an aspect provided herein, is a compound of Formula (I):

, or a pharmaceutically acceptable salt thereof. $R^1$ and $R^2$ are independently ethyl or n-propyl. $R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. $R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, , , , or , , , or . $R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–In embodiments, the inhibitor forms an irreversible bond with the amino acid residue. In embodiments, the bond is a covalent bond.

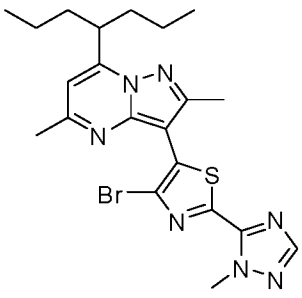
**[0171]** In certain embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl.

**[0172]** In certain embodiments, $R^3$ is Cl, Br, or methyl.

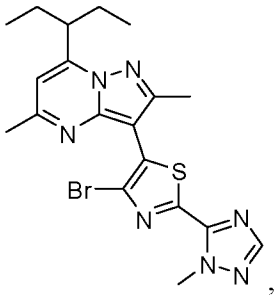
**[0173]** In certain embodiments, $R^4$ is Br, $R^aR^bN$–, pyridin-4-yl, morpholin-4-yl, or , .

**[0174]** In certain embodiments, $R^4$ is morpholin-4-yl or .

**[0175]** In certain embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$– and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

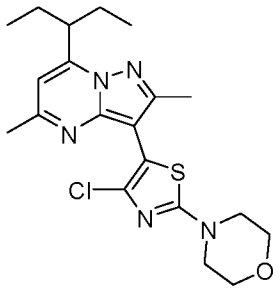
**[0176]** In certain embodiments, the compound is , or a pharmaceutically acceptable salt thereof.

**[0177]** In certain embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

**[0178]** In certain embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

**[0179]** In one aspect described herein, there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

**[0180]** In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof; and repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of said astressin.

**[0181]** In one aspect described herein, there is a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

**[0182]** In one aspect described herein, there is a method of improving quality of life in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

## III. Pharmaceutical Compositions

**[0183]** In an aspect, there is provided a pharmaceutical composition, including a compound as described herein, including embodiments, or the structural Formula (I), and a pharmaceutically acceptable excipient.

**[0184]** The compounds (e.g., $CRF_1$ inhibitors/antagonists) of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are "pharmaceutical compositions" comprising a compound (e.g., $CRF_1$ inhibitor(s)/ antagonist(s)) and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In certain embodiments, the compound (e.g., $CRF_1$ inhibitor/antagonist) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

**[0185]** In one aspect described herein, there is a pharmaceutical composition in the form of a capsule comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a pharmaceutical composition in the form of a tablet comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

**[0186]** The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

**[0187]** The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of $CRF_1$ function) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and

disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

**[0188]** The tablets, capsules and the like suitable for oral administration may be uncoated or coated to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly(methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

**[0189]** Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

**[0190]** Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

**[0191]** Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

**[0192]** Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

**[0193]** The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

**[0194]** The pharmaceutical compositions typically comprise a therapeutically effective amount of a $CRF_1$ inhibitor/antagonist contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-

Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

**[0195]** After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

**[0196]** Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a $CRF_1$ inhibitor/antagonist, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

**[0197]** Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., $CRF_1$ inhibitor/antagonist) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

**[0198]** The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

**[0199]** The present disclosure contemplates the administration of the compound (e.g., $CRF_1$ inhibitor/antagonist) in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

**[0200]** The compound (e.g., $CRF_1$ inhibitor/antagonist) contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

## IV. Methods

**[0201]** In certain embodiments, provided herein are methods for treating or preventing a disease comprising administering an effective amount of a compound of Formula (I), or an isotopic variant thereof or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

**[0202]** In one embodiment, provided herein are methods for treating or preventing a tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a benign tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a malignant tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal rest tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

**[0203]** In one embodiment, provided herein are methods for treating or preventing infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing male infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm count, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm

motility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm morphology, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing female infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

**[0204]** In one embodiment, provided herein are methods for treating or preventing a proliferative or hyperproliferative disease or disorder, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a cancer of the breast, skin, prostate, cervix, uterus, ovary, testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system.

**[0205]** In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenstrom's macroglobulinemia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem

glioma, ependymoma, aligodendrogliorna, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mutinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prol actin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcorna; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland

cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but not limited to, renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (*See* Fishman *et al.*, 1985, *Medicine*, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy *et al.*, 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

**[0206]** Depending on the disorder, disease, or condition to be treated, and the subject's condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration as described elsewhere herein.

**[0207]** The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. Recommended routes of administration for the second active agents are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

**[0208]** In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

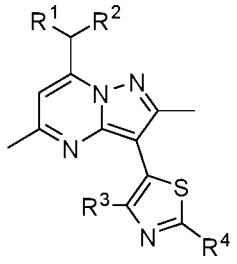
**[0209]** In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I),

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

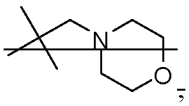
**[0210]** In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

**[0211]** In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

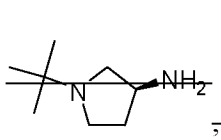
**[0212]** In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):



, or a pharmaceutically acceptable salt thereof. $R^1$ and $R^2$ are independently ethyl or n-propyl. $R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. $R^4$ is hydrogen, Br, $R^aR^bN$–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



;



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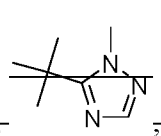
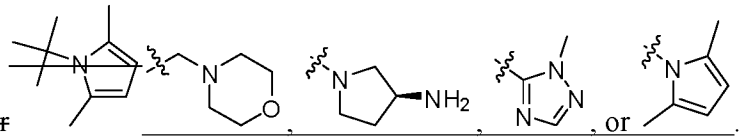


~~, or~~



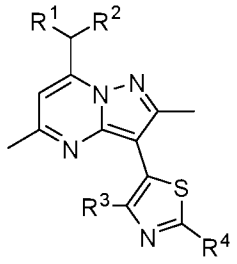
, or



.

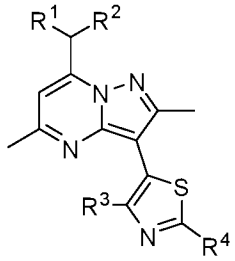
$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

**[0213]** In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



, or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments.

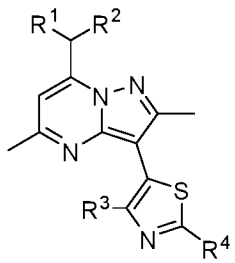
**[0214]** In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):



, or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 60% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 70% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 80% of the subjects demonstrate reduction in ACTH. In embodiments, at least about 10% of subjects were in the standard or normal range for ACTH after treatment.

**[0215]** In embodiments, at least about 20% of subjects were in the standard or normal range for ACTH after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for ACTH after treatment. In certain embodiments, ACTH levels are decreased or reduced within about 30 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 1 hour post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

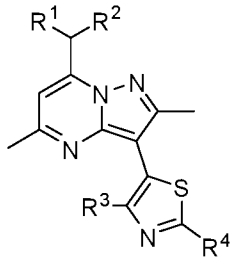
**[0216]** In an aspect provided herein, is a method of decreasing or reducing 17α-hydroxyprogesterone (17-OHP) levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):



, or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 60% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 70% of the subjects demonstrate reduction in

17-OHP. In certain embodiments, at least about 80% of the subjects demonstrate reduction in 17-OHP. In embodiments, at least about 30% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 60% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 60% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment.

**[0217]** In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

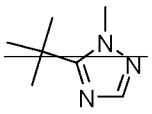
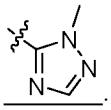


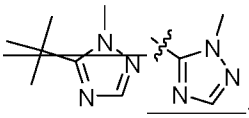
, or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 60% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 70% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 80% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 90% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least 100% of the subjects demonstrate reduction in androstenedione. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least 60% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range

for androstenedione after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range for androstenedione after treatment.

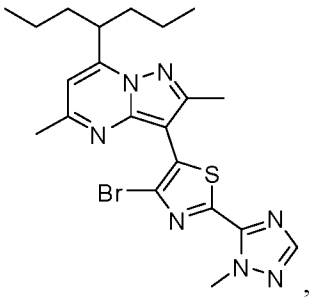
**[0218]** In certain embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl.

**[0219]** In certain embodiments, $R^3$ is Cl, Br, or methyl.

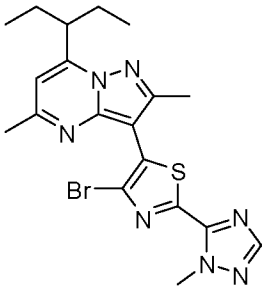
**[0220]** In certain embodiments, $R^4$ is Br, $R^aR^bN$–, pyridin-4-yl, morpholin-4-yl, or 
.

**[0221]** In certain embodiments, $R^4$ is morpholin-4-yl or .

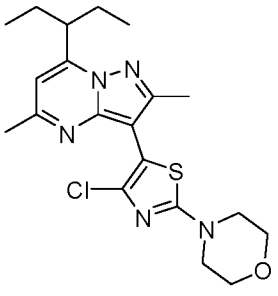
**[0222]** In certain embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$– and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

**[0223]** In certain embodiments, the compound is , or a pharmaceutically acceptable salt thereof.

**[0224]** In certain embodiments, the compound is

, or a pharmaceutically acceptable salt thereof.

**[0225]** In certain embodiments, the compound is

, or a pharmaceutically acceptable salt thereof.

**[0226]** In certain embodiments, a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is cyclically administered to a patient. Cycling therapy involves the administration of an active agent or a combination of active agents for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

**[0227]** In certain embodiments, in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein (e.g., treatment or prevention of testicular adrenal rest tumors (TART) or treatment or prevention of ovarian adrenal rest tumors (OART)), an appropriate dosage level of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof generally is ranging from about 1 mg to 3000 mg, from about 1 mg to 2000 mg, from about 1 mg to 1000 mg, from about 1 mg to about 500 mg, from about 5 mg to about 500 mg, from about 5 mg to about 400 mg, from about 5 mg to about 300 mg, from about 5 mg to about 250 mg, from about 5 mg to about 200 mg, from about 50 mg to about 200 mg, from about 10 mg to about 400 mg, from about 5 mg to about 25 mg, from about 10 mg to about 25 mg, or from about 25 to about 200 mg, which can be administered in single or multiple doses. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is

administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg/day.

**[0228]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg.

**[0229]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, or about 1000 mg.

**[0230]** For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing from about 1.0 mg to about 1,000 mg of

a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof for the symptomatic adjustment of the dosage to the patient to be treated. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the

form of tablets or capsules containing about 50 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 200 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.The pharmaceutical compositions can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg,

about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about

545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered three times per day.

**[0231]** In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of one day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of two days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of three days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of four days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of five days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of six days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of seven days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of eight days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of nine days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of ten days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 11 days. In some

embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 12 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 13 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 14 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 15 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 16 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 17 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 18 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 19 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 20 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 21 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 22 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 23 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 24 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 25 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 26 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 27 days. In some embodiments, the compound of

Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 28 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 29 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 30 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 31 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 32 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 33 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 34 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 35 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 36 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 37 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 38 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 39 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 40 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 41 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 42 days or more.

**[0232]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 25 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days.

**[0233]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least

about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 14 days.

**[0234]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period

of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily

for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 14 days.

**[0235]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant

thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280

mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant

thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 28 days.

**[0236]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 50 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula

(I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 500 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 28 days.

**[0237]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 255 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 42 days. In certain embodiments, the

compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is

administered in an amount of about 310 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 42 days. In certain embodiments, the

compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 42 days.

**[0238]** In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or

prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 42 days. In certain

embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or

prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 42 days.

**[0239]** In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, or about 800 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered at least once per day.

**[0240]** In certain embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

**[0241]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

**[0242]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

**[0243]** In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

**[0244]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a

pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject.In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day.

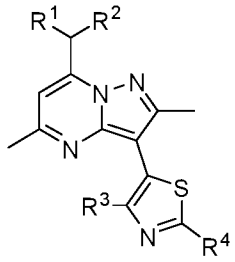
**[0245]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

**[0246]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 6 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 5 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 3 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 1 hour before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

**[0247]** In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

**[0248]** In another aspect is provided a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I): and a pharmaceutically acceptable excipientcomprising with a compound as described herein,

including embodiments, or the structural Formulae (I) and a pharmaceutically acceptable excipient:



, or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$, and $R^4$ are as described herein, including embodiments.

**[0249]** In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0250]** In certain embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0251]** In certain embodiments, the pharmaceutical composition is administered orally.

**[0252]** In certain embodiments, the pharmaceutical composition is formulated as a capsule or tablet. In certain embodiments, the capsule or tablet comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg,

about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 50 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 200 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

**[0253]** In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

**[0254]** In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

**[0255]** In certain embodiments, the pharmaceutical composition is administered in the fed state. In certain embodiments, the pharmaceutical composition is administered in the fasted state. In certain embodiments, the pharmaceutical composition is administered at least once per day.

**[0256]** In certain embodiments, the pharmaceutical composition is administered at bedtime. In certain embodiments, the pharmaceutical composition is administered less than about 6 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 5 hours before sleep. In certain embodiments, the pharmaceutical composition is

administered less than about 4 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 3 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 1 hour before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep.

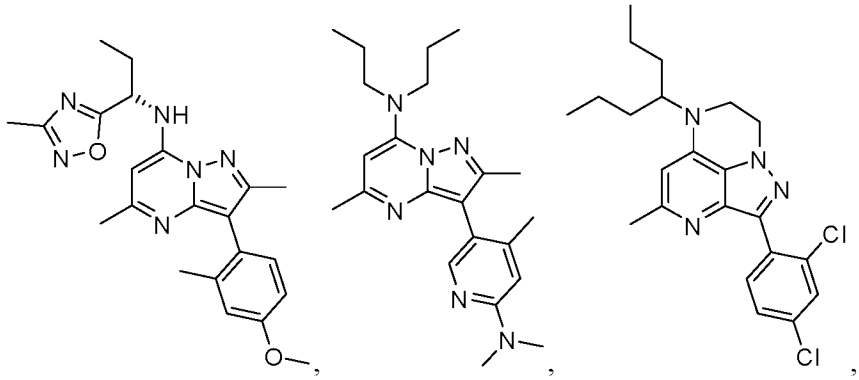
**[0257]** In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

**[0258]** In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

**[0259]** In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

**[0260]** In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

**[0261]** In certain embodiments, the the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In certain embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In certain embodiments, the mineralocorticoid is fludrocortisone. In certain embodiments, the additional chemotherapeutic agent is another $CRF_1$ antagonist. In certain embodiments, the $CRF_1$ antagonist is: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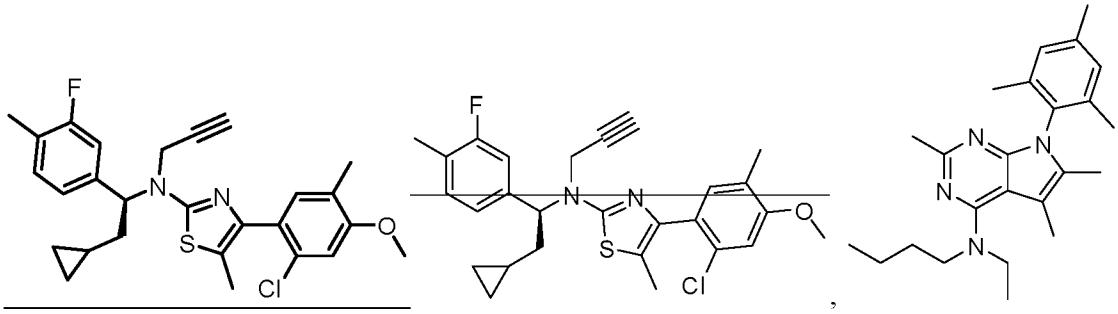
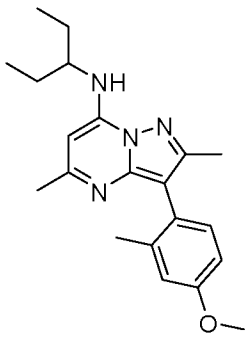
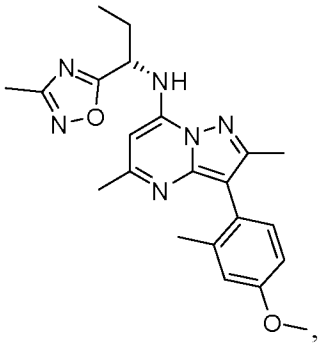

, or



, or a pharmaceutically acceptable salt thereof. In certain embodiments, the $CRF_1$ antagonist is , or a pharmaceutically acceptable salt thereof.

**[0262]** In certain embodiments of the methods disclosed herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In certain embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0263]** In certain embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the radiation therapy is prior to administration of the $CRF_1$ antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is

concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

**[0264]** In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. In some embodiments, a tablet comprises a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil, or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. In some embodiments, a capsule comprises a solid carrier such as gelatin.

**[0265]** In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer's injection, or Lactated Ringer's injection. In some embodiments, preservatives, stabilisers, buffers, antioxidants, and/or other additives are included as required.

**[0266]** In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

**[0267]** The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, 2nd Edition, Rathbone *et al.*, Eds., Marcel Dekker, Inc.: New York, NY, 2008).

**[0268]** The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s)

sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

**[0269]** The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

**[0270]** In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

**[0271]** The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

**[0272]** Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage

of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

**[0273]** Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

**[0274]** Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

**[0275]** Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil,

including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

**[0276]** Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

**[0277]** It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

**[0278]** The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients

from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

**[0279]** The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

**[0280]** The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

**[0281]** Coloring and flavoring agents can be used in all of the above dosage forms.

**[0282]** The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

**[0283]** The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral

administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

**[0284]** The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

**[0285]** The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

**[0286]** Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methy1-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

**[0287]** Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl-and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable

emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

**[0288]** When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungi static concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

**[0289]** In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

**[0290]** The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

**[0291]** The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

**[0292]** Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and metliacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

**[0293]** Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

## V. Examples

**[0294]** While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

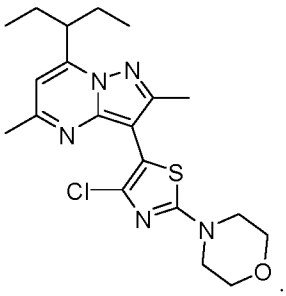
### Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors

**[0295]** Testicular adrenal rest tumors (TART) is a common complication in congenital adrenal hyperplasia (CAH) that is caused by adrenocorticotropin hormone (ACTH)–driven overstimulation of aberrant adrenal cells within the testes and results in impaired spermatogenesis and infertility. TARTS can be found anywhere on the testes, though a typical (very common) location is within the mediastinum. This is a particularly problematic location. Because of the central location of TARTs being in the mediastinum, compression of the nearby seminiferous tubules is common and can lead to obstructive azoospermia, irreversible damage to surrounding tissue, and permanent infertility in males.

**[0296]** Current treatment for TART consists of chronic high-dose glucocorticoids, a problematic therapy with significant side effects and a narrow therapeutic window. Given the serious nature of TART and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with TART. Compound 1, a high-affinity and selective small-molecule antagonist of the corticotropin-releasing factor type-1 ($CRF_1$) receptor, may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH (FIG. 12A-12B). Compound 1 has been

shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. These promising results provide a rationale for investigating the use of Compound 1 in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.

**[0297]** The structure of Compound 1 is:




**[0298]** Building upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2 proof-of-concept study of Compound 1 in subjects with CAH, this Phase 2 will study Compound 1 specifically in male CAH subjects with TART for the first time. A sample size of approximately 12 subjects was selected to provide sufficient data for an initial evaluation of efficacy and safety in subjects with TART while maintaining feasible subject recruitment goals for this rare condition. Given the rarity of the disease and thus the small sample size that can be recruited, this study will be open label, and all enrolled subjects will receive active study drug. Subjects will serve as their own controls in that their outcome measures after 12 weeks of study drug dosing will be compared to their baseline measures.

**[0299]** The schedule of study visits (every 2 weeks through Week 4, then every 4 weeks for the remainder of the study) provides an appropriate balance between minimizing subject burden and closely monitoring subject safety and response to therapy. The 4-week post-treatment washout period will allow for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

**[0300]** The specification of study drug dosing at 10pm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers. The plasma $C_{max}$ (maximum concentration) for Compound 1 in the Phase 1 studies occurred approximately 5 hours after dosing. Therefore, Compound 1 will be dosed daily at 10pm in this study in order to achieve peak plasma study drug concentration at the time of day when most adrenal androgens are produced. Subjects will consume a standardized snack before taking study drug because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety. (**FIGS. 1A-1B**).

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the efficacy of Compound 1 in subjects with TART | • Reduction in the size/volume of TART on testicular ultrasound from screening to Week 12 |
| **Secondary** | |
| • To evaluate the safety of Compound 1 in subjects with TART | • Adverse events (AEs), serious adverse events (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs)<br>• Physical examination findings<br>• Vital signs<br>• Changes in electrocardiogram (ECG)<br>• Changes in clinical laboratory values |
| • To assess the pharmacodynamic (PD) biomarker effects of Compound 1 | • Changes in plasma concentrations of key PD biomarkers, including ACTH, 17-OHP, testosterone, androstenedione, luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone–binding globulin (SHBG), renin, and aldosterone from baseline to Week 12 |
| • To assess changes on semen analysis | • Changes in sperm count, morphology, and motility from baseline to Week 12 |
| • To assess changes in metabolism | • Changes in metabolic parameters, including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12<br>• Changes in body weight, body mass index (BMI), waist circumference, and blood pressure |
| • To evaluate changes in quality of life (QoL) and mood | • Changes in QoL measured using the Short Form 36 (SF-36)<br>• Changes in mood measured using the Hospital Anxiety and Depression Scale (HADS) |

**Study Population**

**[0301]** Approximately 12 male subjects with TART will be enrolled at approximately 6 investigative sites in the United States, United Kingdom, and possibly other countries. Up to 12 additional subjects may be added to further evaluate specific safety, PD, or efficacy findings.

**Eligibility Criteria**

Inclusion Criteria

- Adult male subjects aged 18 to 30, inclusive
- Documented historical diagnosis of CAH based on documented genetic mutation or historical documentation of elevated 17-OHP
- Diagnosis of TART via testicular ultrasound and/or magnetic resonance imaging (MRI) at screening with ≥1 lesion(s) measuring ≥2 cm in diameter
- On a stable regimen of GC replacement for ≥30 days before baseline
- Agree to follow contraception guidelines and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug
- Subject is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Exclusion Criteria

- Any clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
  - A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
  - Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m$^2$
  - Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
  - Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
- Any clinically significant psychiatric disorders, including any current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months
- HADS score >12 for either depression or anxiety
- At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at screening and baseline (eg,

C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)

- Clinically significant and abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:
  - Clinically meaningful abnormal ECG results, in the opinion of the Investigator
  - Fridericia-corrected QT interval (QTcF) >450 msec
  - Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
  - Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- A history that includes bilateral adrenalectomy or hypopituitarism
- Use of any other investigational drug within 30 days or 5 half-lives, whichever is longer, before initial screening
- Require use of prohibited concomitant medications, including strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids, hydrocortisone, and dexamethasone) within 30 days or 5 half-lives (whichever is longer) of first dose of study drug. Medications that are sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
- Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

**Study Duration**

**[0302]** The expected duration of study participation for each subject is up to approximately 20 weeks. This includes a screening period of ≤4 weeks, a treatment period of 12 weeks, and a safety follow-up period of 4 weeks.

**Study Design**

**[0303]** This is a Phase 2, open-label efficacy and safety study of Compound 1 for the treatment of TART. All subjects will receive a daily oral dose of Compound 1 for 12 weeks.In-clinic study visits will occur for screening and at Day 1 (baseline) and Weeks 2, 4, 8, 12 (end of treatment), and 16 (follow-up).

**Dose, Route, Regimen**

**[0304]** All subjects will receive a daily oral dose of Compound 1 for 12 weeks. Subjects will receive 600 mg/day during the first 2 weeks and 1000 mg/day during the remaining 10 weeks of the treatment period. Study drug will be taken daily at 10pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

**[0305]** On mornings of study visits with 8am blood draws for laboratory assessments, subjects should take their morning glucocorticoid replacement after the blood draws. For all other days during the study, subjects may take their morning glucocorticoid replacement at their usual time (generally between 6am and 8am).

**[0306]** If a subject experiences a Grade 3 or higher TEAE considered at least possibly related to study drug, the Investigator may reduce the subject's daily dose of Compound 1 down in increments of 200 mg. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria.

**Investigational Drug**

**[0307]** Compound 1 is a small-molecule $CRF_1$ receptor antagonist and will be supplied as 200-mg, size 1, white, hard gelatin capsules.

**Example 2.**

**[0308]** Since elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1, a small-molecule antagonist of the $CRF_1$ receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. 12A-12B). The safety profile of Compound 1 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH is currently ongoing.

*Nonclinical Toxicology of Compound 1*

**[0309]** The nonclinical safety profile of Compound 1 has been evaluated in repeat-dose range-finding and definitive toxicology studies of up to 91 days in duration in rats and dogs using the clinically relevant route (oral) and schedule of administration (once daily). In rats and beagle dogs administered oral Compound 1 once daily for 91 consecutive days at doses up to 2000 mg/kg/day, toxicologic findings were all mild and limited to the male reproductive tract, and all Compound 1-related findings were reversible following a 6-week treatment-free recovery period.

**[0310]** Additionally, a fertility toxicology study was conducted in rats. In this study, male rats were administered oral Compound 1 once daily at 0, 5, 20, or 1000 mg/kg for 85 to 87 days (70 days before mating, during mating, and ≤4 days between mating and necropsy). Male reproductive performance (mean day of mating, mating and fertility indices, and conception rates) was unaffected by Compound 1 treatment. Untreated females mated with the Compound 1-treated males had no ovarian and uterine effects.

**[0311]** In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay have also been conducted.

*Clinical Experience with Compound 1*

**[0312]** To date, a total of 53 subjects, all healthy adults aged 21 to 65 years, have been treated with at least 1 dose of Compound 1 in 2 Phase 1 studies. The first-in-human study of Compound 1 (Study I3C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study I3C-FW-BLAB) evaluated repeat doses of 50 mg, 100 mg, or 200 mg Compound 1 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs). Compound 1 has been well tolerated in healthy human subjects, with no SAEs, AEs leading to discontinuation, or dose-limiting toxicities (DLTs). A maximum tolerated dose has not been reached in humans.

**[0313]** An ongoing Phase 2 open-label study (Study Compound 2) is currently evaluating the safety and efficacy of Compound 1 dosed once daily for 6 weeks in adults with classic CAH. In the initial Cohort A of this study, all subjects are dosed starting at 200 mg/day for 14 days, escalating for each subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLTs at the previous dose level. (**FIGS. 2-3**).

*Known Potential Risks*

**[0314]** Because the reversible testicular effects (degeneration/atrophy) observed in rats and dogs treated with high-dose Compound 1 (2,000 mg/kg/day) are likely associated with on-target (mechanism-driven) effects, these effects are likely to be relevant to human risk. However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical laboratory markers of testicular function (LH and FSH) when Compound 1 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Clinical laboratory measures

of testicular function (LH, FSH, inhibin B, and SHBG) will be assessed throughout this study to monitor the risk of testicular injury. Testicular ultrasounds and semen analysis will also be performed at screening/baseline and the end of the treatment period.

**[0315]** Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the Phase 1 clinical studies. Clinical laboratory measures of liver chemistry will be assessed throughout this study, and strict individual treatment stopping criteria for liver chemistry findings are in place.

**[0316]** Compound 1-induced effects on the thyroid gland were noted in dogs after 91 days of high-dose (2,000 mg/kg/day) treatment but not in any other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) were not evaluated in the Phase 1 studies but will be monitored throughout this study.

*Known Potential Benefits*

**[0317]** Early clinical studies suggests that Compound 1 is effective as a $CRF_1$ receptor antagonist, a mechanism of action that supports the clinical investigation of Compound 1 for treatment of TART. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. 12A-12B).

*Assessment of Potential Risks and Benefits*

**[0318]** The mild and reversible toxicologic effects of Compound 1 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a $CRF_1$ receptor antagonist, Compound 1 is intended to reduce abnormally elevated ACTH levels, which in TART drives overstimulation of aberrant adrenal cells within the testes. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. In TART, where baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

**[0319]** Given the serious nature of TART and the limitations (and risks) of chronic steroid therapy, new treatment modalities are needed for patients with TART. Given the acceptable safety and tolerability profile of Compound 1 in healthy volunteers from the Phase 1 program, the low probability of demonstrating meaningful PD marker changes in healthy subjects, and the lack of any clear benefit to exposing more healthy subjects to study drug, the Sponsor believes the benefit-to-risk profile favors the entry of Compound 1 into Phase 2 in subjects with TART.

**Example 3. Congenital Andrenal Hyperplasia (CAH)**

**[0320]** CAH results from a genetic defect in the 21-hydroxylase enzyme. CAH patients are thus unable to produce cortisol. Without cortisol to provide negative feedback, patients over-produce ACTH. High ACTH promotes the overproduction of potent androgens (male sex hormones). Without wishing to be bound by theory, Compound 1 blocks $CRF_1$ receptor to prevent ACTH release by the pituitary and associated drive on the hypothalamic-pituitary-adrenal axis. Replacement of cortisol to physiological levels will correct cortisol deficiency, however, will not lower ACTH, resulting in hyperplasia of adrenal gland and associated overproduction of adrenal androgens.

**[0321]** As shown in **FIGS. 4** and **5A-5B**, the attenuation of ACTH demonstrates target engagement and functional $CRF_1$ receptor antagonism. 80% of subjects demonstrated reduction in ACTH. 70% of subjects demonstrated > 25% reduction in ACTH. 30% of subjects were in the normal range (*) after treatment with a $CRF_1$ receptor antagonist.

**[0322] FIGS. 6** and **7A-7B** demonstrate "control" of disease based on standard guidelines, which would then allow steroid taper. 80% of subjects demonstrated reduction in 17-OHP. 50% of subjects demonstrated > 25% reduction in ACTH. 50% of subjects were in the guideline range (*; 1200 ng/dL) after treatment with a $CRF_1$ receptor antagonist.

**[0323] FIGS. 8** and **9A-9B** demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess ~~andreogen~~ androgen production and associated symptoms. 100% of subjects demonstrated reduction in androstenedione (at various doses). 60% of subjects demonstrated > 25% reduction in androstenedione. 50% of subjects were within the normal reference range after treatment with a $CRF_1$ receptor antagonist.

**[0324] FIGS. 10A-10B** show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a $CRF_1$ receptor antagonist.

**[0325] FIGS. 11A-11B** demonstrate Compound 1 is a potent, selective, and functional $CRF_1$ receptor antagonist. In in vitro and ex vivo studies, Compound 1 was determined to be a potent and selective $CRF_1$ receptor antagonist with high affinity and selective for the $hCRF_1$ receptor. Compound 1 was found to have functional potency to inhibit adenylate cyclase activity ($CRF_1$ receptor-mediated downstream cascade), demonstrating in vitro efficacy as a $CRF_1$ receptor antagonist. Compound 1 was found to significantly inhibit CRF-induced locomotor behavior in response to i.c.v. administration of CRF (**FIG. 11B**).

**[0326]** ~~**FIGS. 12A-12B** demonstrate single pill of $CRF_1$ receptor antagonist improves ACTH and 17-OHP in CAH patients.~~ **FIGS. 12A-12B** demonstrate single pill of $CRF_1$ receptor

antagonist (i.e., as described in US 2017/0020877 A1) improves ACTH and 17-OHP in CAH patients.

**[0327] FIG. 13** shows the subject level hormone changes (ACTH, 17-OHP, and androstenedione) by dose of a $CRF_1$ receptor antagonist.

**Example 4. Assess reduction in excess ACTH and adrenal steroid production**

**[0328]** The objectives of the study are: to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable gluococorticoid regimen; to evaluate the safety and tolerability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

**ELIGIBILITY CRITERIA**

**[0329]** Inclusion Criteria:

- Adult males and females 18 years or older
- Diagnosis of classic CAH due to 21-hydroxylase deficiency
- Morning 17OHP ≥800 ng/dL, before taking any morning GC dose
- On a stable regimen of gluococorticoid replacement for ≥30 days before enrollment

**[0330]** Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease within 30 days of screening
- Clinically significant psychiatric disorder
- History of bilateral adrenalectomy or hypopituitarism

**STUDY DESIGN**

**[0331] FIG. 14** depicts the proof of concept and escalating QD dosing at 10 PM for Cohort A and the single dose level and BID dosing at 10 AM and 10 pm for Cohort B.

**BASELINE CHARACTERISTICS**

**[0332]** Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 partcipants were enrolled and received at least 1 dose of Compound 1. One participant withdrew early because of an occupation-related scheduling conflict. In Cohort B, 9 participants were enrolled and received at least one dose of Compound 1. One participant was withdrawn upon discovery of a major protocol violation at Baseline and did not have postbaseline efficacy/PK data. Thus, baseline characteristics are calculated for n=8 in Cohort B. One participant in Cohort B was taking both HC and prednisone.

*Table 1 – Baseline characteristics of each cohort*

| Parameter | Cohort A (n=10) | Cohort B (n=8) |
|---|---|---|

| | | |
|---|---|---|
| Demographics<br>Age (years), mean (range)<br>Sex<br>Bmi (kg/m$^2$), mean ± SD | <br>39.3 (24-66)<br>5M, 5F<br>31.5 ± 12.0 | <br>36.8 (19-66)<br>1M, 7F<br>31.1 ± 6.7 |
| Daily GC dose (mg HC equivalents), mean range<br>Types of GCs | <br>28 (13-40)<br>4 JC, 3 pred, 3 dex | <br>35 (20-50)<br>2HC, 4 pred, 3 dex |
| 17OHP at screening[a] (ng/dl), mean ± SD | <br>5,985 ± 6,347 | <br>4,592 ±4,624 |

Abbreviations: 17OHP: 17-hydroxyprogesterone; BMI: body mass index; dex: dexamethasone; F: female; GC: glucocorticoid; HC: hydrocortisone; M: male; pred: prednisone; SD: standard deviation.
a 17OHP reference ranges: 27-199 ng/dL males, 15-290 ng/dL females.

**SAFETY**

**[0333]** Across both cohorts, Compound 1 was generally well tolerated. The most common type of adverse event (AE) was gastrointestinal disorders There were no serious AEs and no AEs leading to withdrawal.

**PHARMACOKINETICS**

**[0334]** Over a wide range of doses (200 to 1000 mg QD), Compound 1exhibited a predictable, dose-dependent PK profile.

**EFFICACY**

**[0335] FIG. 15A-15D** show the changes in levels of Androstenedione (A4) across both cohorts. Levels of A4 improved at ≥1 dose level for 10 out of 10 participants in Cohort A and 6 out of 8 participants in Cohort B. Excess A4 is associated with clinical sequelae in CAH. Attenuation of A4 demonstrates control of adrenal androgen.

**[0336] FIG. 16A-16D** show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 6 out of 7 participants in Cohort B. 17OHP is a critical hormone in CAH diagnosis and management. Attenuation of 17OHP demonstrates control of adrenal steroid production.

**[0337] FIG. 17A-17D** show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 5 out of 7 participants in Cohort B. Attenuation of ACTH demonstrates target engagement and fucntional $CRF_1$ receptor antagonism.

*Table 2 – Percentage change from baseline in ACTH, 17OHP and A4.*

| | Cohort A | | | Cohort B |
|---|---|---|---|---|
| | 200 mg QD (Week 2) | 600 mg QD (Week 4) | 1000 mg QD (Week 6) | 200 mg BID (~~Weed~~ Week 2) |
| ACTH | -25.7 (±51.6) | -60.1 (±37.5) | -32.7 (±47.0) | -36.5 (±58.0) |
| 17OHP | +22.2 (±172.3) | -23.7 (±64.2) | -13.8 (±74.7) | -47.8 (±63.3) |
| A4 | -12.1 (±47.4) | -33.2 (±36.5) | -28.6 (±44.6) | -16.0 (±81.4) |

**CONCLUSIONS**

**[0338]** Compound 1, a potent and selective $CRF_1$ receptor antagonist, offers a novel nonsteroidal oral treatment approach for CAH. Compound 1 was well tolerated and efficacious in reducing excess ACTH, 17OHP, and androstenedione in patients with classic CAH. Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

**[0339]** While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re the Application of:<br><br>Inventors: Alexis Howerton et al.<br><br>Application No.: 19/043,275<br><br>Filing Date: January 31, 2025<br><br>Title: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS | Confirmation No.: 5486<br><br>Art Unit: 1627<br><br>Examiner: Pihonak, Sarah<br><br>Customer No.: 21971<br><br>Certificate of Electronic Filing<br>I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office's electronic filing system to the USPTO on August 15, 2025.<br><br>By: / Colleen Mensching /<br>Colleen Mensching |

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION**

Dear Commissioner:

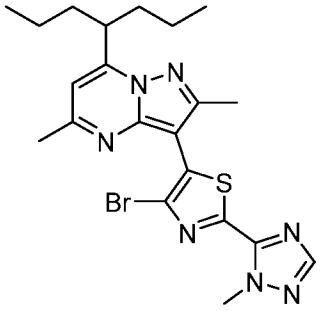
In response to the Non-Final Office Action mailed May 30, 2025, setting an initial due date of August 30, 2025, Applicant respectfully requests reconsideration of the above-referenced application in view of the following amendments and remarks. This response is timely filed.

**Amendments to the Claims** begin on page **2** of this paper.
**Amendments to the Specification** begin on page **6** of this paper.
**Summary of the Interview** begins on page 7 of this paper.
**Remarks** begin on page **8** of this paper.
**Conclusion** begins on page **10** of this paper.

## AMENDMENTS TO THE CLAIMS

### Listing of the Claims

1. (**Currently Amended**) A method of treating an endocrine disorder associated with corticotropin-releasing factor type-1 ($CRF_1$) activity, comprising administering to a subject in need thereof a small molecule $CRF_1$ antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule $CRF_1$ antagonist is: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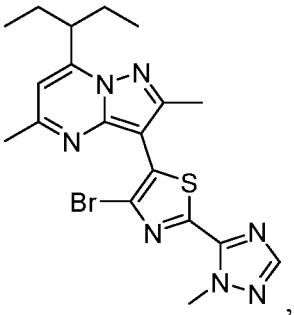
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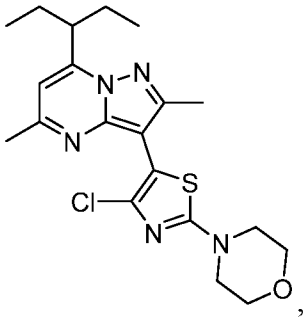
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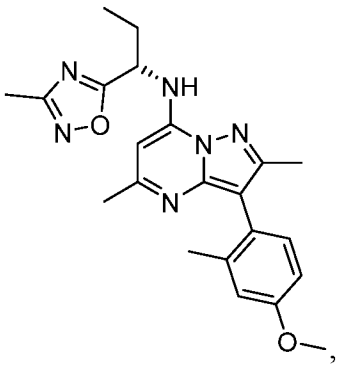
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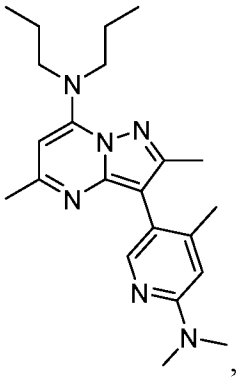
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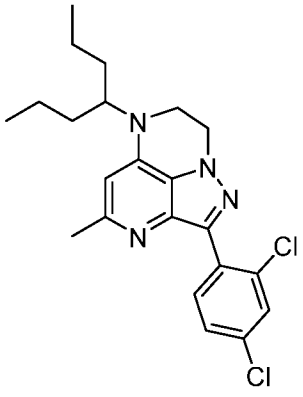
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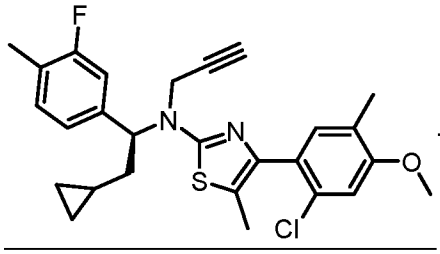
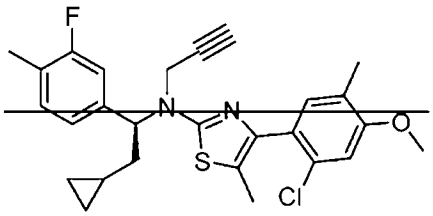
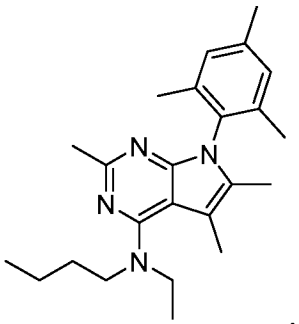
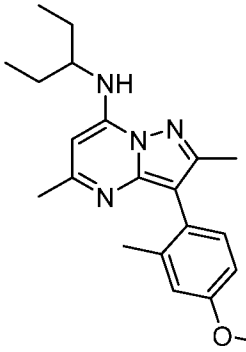
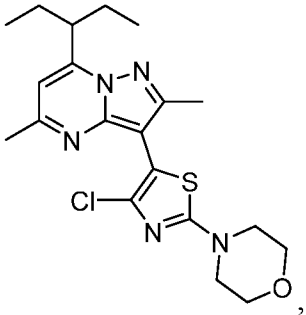





or , or a pharmaceutically acceptable salt thereof,

wherein the small molecule $CRF_1$ antagonist is administered to the subject twice per day, and

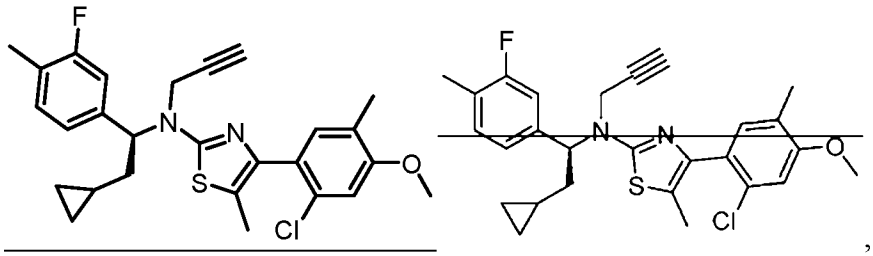
wherein the subject is in the fed state.

2. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is:



, or a pharmaceutically acceptable salt thereof.

3. (**Currently Amended**) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is:



, or a pharmaceutically acceptable salt thereof.

4. (Original) The method of claim 1, wherein the endocrine disorder associated with $CRF_1$ activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).
5. (Original) The method of claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).
6. (Original) The method of claim 1, wherein the subject is receiving a glucocorticoid in conjunction with the administering of the small molecule $CRF_1$ antagonist.
7. (Original) The method of claim 6, wherein the glucocorticoid comprises beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone, or a combination thereof.
8. (Original) The method of claim 7, wherein the glucocorticoid is hydrocortisone.
9. (Original) The method of claim 1, wherein the subject is an adolescent.
10. (Original) The method of claim 1, wherein the subject is at least 18 years old.
11. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.
12. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 50 mg.
13. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 100 mg.
14. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 200 mg.
15. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 400 mg.
16. (Cancelled)

17. (Cancelled)
18. (Cancelled)
19. (Cancelled)
20. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered orally.
21. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is formulated as a capsule or tablet.
22. (New) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered less than about 6 hours before sleep.
23. (New) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered less than about 3 hours before sleep.
24. (New) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered in the evening.

## AMENDMENTS TO THE SPECIFICATION

Applicant provides herewith both a clean copy and a marked copy of a substitute specification, excluding claims, in compliance with 37 C.F.R. §§ 1.52, 1.121, and 1.125. The amendments follow the Certificate of Correction (submitted on March 12, 2025, and accepted by the U.S. Patent Office on June 17, 2025) for U.S. Pat. No. 11,304,950.

Applicant respectfully requests that the specification of record be replaced with the substitute specification filed herewith.

## SUMMARY OF THE INTERVIEW

Applicant is appreciative of Examiner Pihonak for extending the courtesy of a videoconference interview with Applicant's representatives, Victoria Cheng (Reg. No. 79,641) and Kaia Parenti (Reg. No. 81,050), on August 6, 2025.

During the interview, proposed claim amendments were discussed. Agreement was reached that the amendments would overcome the novelty and obviousness rejections.

## REMARKS

Claims 1-21 were pending prior to entry of the amendments presented in this response. Claims 1 and 3 are herein amended. Claim 1 has been amended to incorporate the subject matter of claims 17 and 19. New claims 22-24 have been added, for which support can be found in the as-filed specification (now published as U.S. Pub. No. 2025-0177404), at least at ¶¶ [0263], [0274]. Claims 16-19 are herein canceled without prejudice or disclaimer. No new matter is believed to be added by any of these amendments.

### 35 U.S.C. § 102 Novelty

Claims 1, 3, 5-8, 10-12, 15-16, and 20-21 are rejected as allegedly being anticipated by Grigoridadis (U.S. Pub. No. 2017-0020877; hereafter "Grigoriadis"), as evidenced by El-Maouche et. al., *Lancet*, vol. 309, pp. 2194-2210, publ. 2017 (hereafter "El-Maouche").

Applicant has amended claim 1 to incorporate the limitations of dependent claims 17 and 19, which were not rejected as lacking novelty. As such, Applicant respectfully submits amended claim 1 is novel over the cited reference and requests withdrawal of the novelty rejection. Similarly, Applicant submits claims 3, 5-8, 10-12, 15-16, and 20-21 are also novel over the cited reference by virtue of their dependencies on amended claim 1.

### 35 U.S.C. § 103 Obviousness

Claims 9 and 13-14 are rejected as allegedly lacking nonobviousness over Grigoridadis, as evidenced by El-Maouche et. al., Lancet, vol. 309, pp. 2194-2210, publ. 2017, as applied to claims 1, 3, 5-8, 10-12, 15-16, and 20-21. Claims 1-2, 10-16, and 20 are rejected as allegedly lacking nonobviousness over Chen et. al. (U.S. Pub. No. 2010-0222339; hereafter "Chen").

Applicant has amended claim 1 to incorporate the limitations of dependent claims 17 and 19, which were not rejected as lacking nonobviousness. As such, Applicant respectfully submits amended claim 1 is nonobvious over the cited references and requests withdrawal of the obviousness rejection. Similarly, Applicant submits claims 3, 5-8, 10-12, 15-16, and 20-21 are also nonobvious over the cited references by virtue of their dependencies on amended claim 1.

**Double Patenting**

Claims 1-17 and 20-21 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-19 of U.S. Pat. No. 11,304,950 B2. Claims 1-3, 6-7, 9-17, and 20-21 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-18 and 20-21 of U.S. Pat. No. 11,858,932 B2 in view of Markopoulos et. al., *J. Clin. Endocrinol. Metab.*, vol. 96(3), pp. 623-631, publ. 2011 (hereafter "Markopoulos") and over claims 1-18 and 20-21 of U.S. Pat. No. 12,098,152 B2 in view of Markopoulos. Claims 1-2, 5-17, and 20-21 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over (1) claims 1-4, 7-9, 11-17, and 20-21 of U.S. Pat. No. 11,311,549 B2; (2) claims 1-4, 7-9, 11-17, 19-24, and 26-27 of U.S. Pat. No. 11,344,557 B2; and (3) claims 1-4, 7-9, 11, and 14-21 of U.S. Pat. No. 11,351,177 B2.

Applicant has amended claim 1 to incorporate the subject matter of claims 17 and 19, which were not rejected under nonstatutory double patenting over the cited patents above. As such, Applicant respectfully requests withdrawal of the rejection and favorable reconsideration.

*Provisional Nonstatutory Double Patenting*

Claims 1-2 and 5-19 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 181-188, 194-195, 198-199, 202, and 204 of copending application 18/078,649. Claims 1-5, 9-15, and 17-21 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 72-91 of copending application 18/941,832. Claims 1-5, 9-17, and 20-21 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-19 of copending application 19/043,303. Claims 1-3, 5, and 9-21 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-21 of copending application 19/043,264.

Applicant has amended claim 1 to incorporate the subject matter of claims 17 and 19, which was not provisionally rejected under nonstatutory double patenting over claims in U.S. App. No. 19/043,303. As such, Applicant respectfully requests withdrawal of the rejection and favorable reconsideration.

Without acquiescing to the rejection, Applicant submits herewith a terminal disclaimer over U.S. App. Nos. 18/078,649, 18/941,832, and 19/043,264.

## CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (858)-350-2240.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 50535-710.304).

Respectfully submitted,

Date: August 15, 2025

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79,641

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone: (650) 493-9300
Customer No. 21971

UNITED STATES
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Alexandria, VA 22313 - 1450
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# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **08/15/2025 06:07:07 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | Victoria Cheng |
| PATENT CENTER # | 71882471 | AUTHORIZED BY | Victoria Cheng |
| CUSTOMER # | 21971 | FILING DATE | 01/31/2025 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | Alexis HOWERTON |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| **DA / 232415** | **E20258EI07388240** | **Victoria Cheng** |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1814 | STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER | 183.00 | 1 | 183.00 |
| | | | **TOTAL AMOUNT:** | **$183.00** |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Alexandria, VA 22313 - 1450
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# APPROVAL LETTER

| APPLICATION # | FILING DATE | APPLICANT/PATENT UNDER REEXAMINATION |
|---|---|---|
| 19/043,275 | 01/31/2025 | Alexis HOWERTON |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

**Electronic terminal disclaimer filed on 08/15/2025**

☑ Approved

**This patent is subject to a Terminal Disclaimer**

**Approved / Disapproved by: Electronic Terminal Disclaimer automatically approved**

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# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **08/15/2025 06:07:07 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | Victoria Cheng |
| PATENT CENTER # | 71882471 | FILING DATE | 01/31/2025 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Victoria Cheng |

## Documents

**TOTAL DOCUMENTS: 2**

| DOCUMENT | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|
| petition-request.pdf | 3 | Terminal Disclaimer-Filed (Electronic) | 46 KB |
| grantLetter.pdf | 1 | Terminal Disclaimer-Electronic-Approved | 18 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| petition-request.pdf | A72669DB50BCB02FD38E95861396072BF4F6D9ECEBCE1E07 4827CDBAC74A5849ED5446D94AA80BFE4BF782F2FA6A4186 B194CC0AD99EA11A49EE272EEBDF0081 |
| grantLetter.pdf | 742AC3A8ABE70A8307F39F5AF2DCF27483D8A17BE59B64195 |

160F204C7C34FBD15393BCCE4BE95BC20447D45BA2D2BABE
ADDC309FF284CD0EEF9ECC0A1C678BD

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

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**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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# TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

| APPLICATION # | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET # |
|---|---|---|---|
| 19043275 | 01/31/2025 | Alexis HOWERTON | 50535-710.304 |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

| | |
|---|---|
| ✓ | Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action |
| ✓ | This electronic Terminal Disclaimer is not being used for a Joint Research Agreement. |

| Owner | Percent interest |
|---|---|
| Spruce Biosciences, Inc. | 100% |
| **Total** | **100%** |

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

| Application # | Filing Date |
|---|---|
| 18078649 | 12/09/2022 |

| | |
|---|---|
| 18941832 | 11/08/2024 |
| 19043264 | 01/31/2025 |

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.
In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

---

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

**Patent #**

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.
In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Terminal disclaimer fee under 37 CFR 1.20(d) included with Electronic Terminal Disclaimer request.

**Applicant claims the following entity status:**
Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statemnts made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I certify, in accordance with 37 CFR 1.4(d)(4) that I am: An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

| Signature | Name | Registration # |
|---|---|---|
| /Victoria Cheng/ | Victoria Cheng | 79641 |

* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP 324.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>19/043,275 | Filing Date<br>01/31/2025 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY:** ☑ LARGE ☐ SMALL ☐ MICRO

## APPLICATION AS FILED - PART I

| FOR | (Column 1)<br>NUMBER FILED | (Column 2)<br>NUMBER EXTRA | | RATE ($) | FEE ($) |
|---|---|---|---|---|---|
| ☐ BASIC FEE<br>(37 CFR 1.16(a), (b), or (c)) | N/A | N/A | | N/A | |
| ☐ SEARCH FEE<br>(37 CFR 1.16(k), (i), or (m)) | N/A | N/A | | N/A | |
| ☐ EXAMINATION FEE<br>(37 CFR 1.16(o), (p), or (q)) | N/A | N/A | | N/A | |
| TOTAL CLAIMS<br>(37 CFR 1.16(i)) | minus 20 = | * | | x $200 = | |
| INDEPENDENT CLAIMS<br>(37 CFR 1.16(h)) | minus 3 = | * | | x $600 = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | | TOTAL | |

## APPLICATION AS AMENDED - PART II

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | 08/15/2025 | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * 20 | Minus | ** 21 | = 0 | | x $200 = | 0 |
| | Independent<br>(37 CFR 1.16(h)) | * 3 | Minus | *** 3 | = 0 | | x $600 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | 0 |

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * | Minus | ** | = | | x $0 = | |
| | Independent<br>(37 CFR 1.16(h)) | * | Minus | *** | = | | x $0 = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | |

| | |
|---|---|
| * If the entry in column 1 is less than the entry in column 2, write "0" in column 3. | SLIE |
| ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". | /DEIDRE C KING-WOODWARD/ |
| *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". | |
| The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1. | |

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

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**United States Patent and Trademark Office**
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 19/043,275 | 01/31/2025 | Alexis HOWERTON | 50535-710.304 | 5486 |

21971 7590 09/12/2025

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER |
|---|
| PIHONAK, SARAH |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1627 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 09/12/2025 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

| Office Action Summary | Application No. 19/043,275 | Applicant(s) HOWERTON et al. | |
|---|---|---|---|
| | Examiner SARAH PIHONAK | Art Unit 1627 | AIA (First Inventor to File) Status Yes |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 8/15/25.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 1-15 and 20-24 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-2,5-15 and 20-24 is/are rejected.

8) ☑ Claim(s) 3-4 is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 1/31/25 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

***Notice of Pre-AIA or AIA Status***

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

***Status of Claims***

1. Claims 1-15 and 20-24 are currently pending as of the response and amendments filed on 8/15/25. Claims 16-19 have been canceled, claims 22-24 have been newly added. The amendments to the specification, filed on 8/15/25 to correct typographical errors are acknowledged and accepted.

The 102(a)(1) and 103 rejections over Grigoriadis as evidenced by El-Maouche are withdrawn in view of the amendments.

The 103 rejection over Chen is withdrawn in view of the amendments.

The nonstatutory double patenting rejections over 18078649, 18941832, and 19043264 are withdrawn in view of the acceptance of the terminal disclaimer filed on 8/15/25. The nonstatutory double patenting rejection over US 11304950 B2, US 11858932 B2, 12098152 B2, US 11311549 B2, US 11344557 B2, US 11351177 B2, and 19043303 are withdrawn in view of the amended claims.

A new rejection under 35 USC 102(a)(2) is made over the claims. As the new rejection is not warranted by the amendments, this action is non-final.

2. Claims 1-15 and 20-24 were examined. Claims 1-2, 5-15, and 20-24 are rejected. Claims 3-4 are objected to.

***Claim Rejections-35 USC § 102***

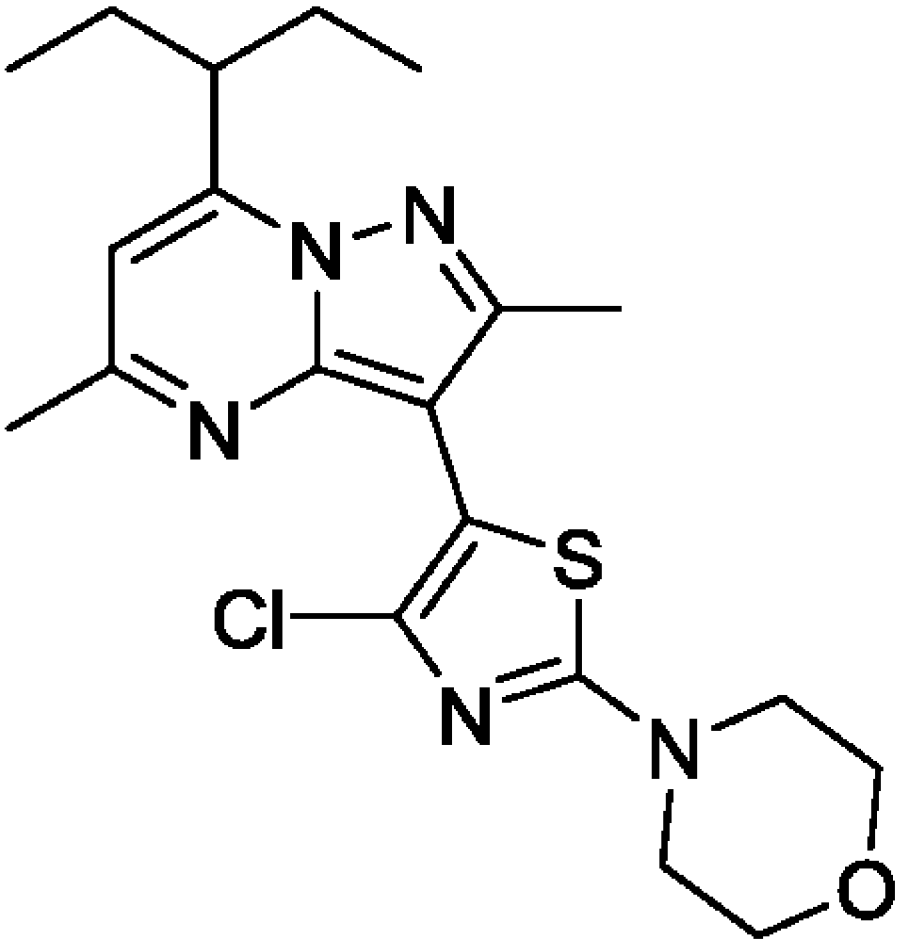
3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

Claim(s) 1-2, 5-15, and 20-24 is/are rejected under 35 U.S.C. 102(a)(2) as being anticipated by Howerton et. al., WO 2019036503 A1, publ. 2/21/2019 (cited in an earlier IDS), claims priority to provisional application 62545406 filed on 8/14/2017, which provides support to the claimed subject matter.

The applied reference has a common inventor with the instant application. Based upon the earlier effectively filed date of the reference, it constitutes prior art under 35 U.S.C. 102(a)(2). This rejection under 35 U.S.C. 102(a)(2) might be overcome by: (1) a showing under 37 CFR 1.130(a) that the subject matter disclosed in the reference was obtained directly or indirectly from the inventor or a joint inventor of this application and is thus not prior art in accordance with 35 U.S.C. 102(b)(2)(A); (2) a showing under 37 CFR 1.130(b) of a prior public disclosure under 35 U.S.C. 102(b)(2)(B) if the same invention is not being claimed; or (3) a statement pursuant to 35 U.S.C. 102(b)(2)(C) establishing that, not later than the effective filing date of the claimed invention, the subject matter disclosed in the reference and the claimed invention were either owned by the same person or subject to an obligation of assignment to the same person or subject to a joint research agreement.

Howerton discloses the corticotropin releasing factor receptor antagonist 3-(4-chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1.5-a)pyrimidine for the treatment of congenital adrenal hyperplasia (CAH), which meets the claim limitation of an endocrine disorder associated with $CFR_1$ activity (title & abstract; para [0003-0004]):




. Howerton discloses administration of the compound for treating CAH by administering the compound shown above, or a pharmaceutically acceptable salt or solvate thereof at a dose between 10 mg/day to 400 mg/day (para [0004-0005], [0091]). Howerton teaches oral administration of the compound in a capsule or tablet composition (para [0007], [0076]), wherein the composition is

administered twice daily (para [0012], [0030]), and wherein the subject is in a fed state (para [0118]). Howerton further discloses administering the compound shown above with a glucocorticoid (para [0013]), wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone (para [0013], [0135-0136]). Howerton additionally discloses administering the compound less than about 4 hours before sleep, or less than 2 hours before sleep, as well as administering the compound in the evening (para [0018]); administration of the compound to a subject from about 12 years old to about 20 years old is also disclosed (para [0039]). Howerton therefore anticipates the claims.

***Claim Objections***

4. Claims 3-4 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Information Disclosure Statement***

5. The IDS filed on 8/13/25 has been considered.

***Conclusion***

6. Claims 1-2, 5-15, and 20-24 are rejected. Claims 3-4 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached Monday-Friday 9:00-5:30 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached at 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SARAH . PIHONAK
Primary Examiner
Art Unit 1627

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 19/043,275 | HOWERTON et al. |
| | Examiner | Art Unit |
| | SARAH PIHONAK | 1627 |

| CPC - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| a61k31/519; a61p5/06,08 | 05/28/2025 | s.p. |
| a61k31/519,5377; a61p5/06,08; a61p35/00 | 09/03/2025 | s.p. |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| | | |

| US Classification - Searched* | | | |
|---|---|---|---|
| **Class** | **Subclass** | **Date** | **Examiner** |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| **Search Notes** | **Date** | **Examiner** |
| a61k31/519; a61p5/06,08 | 05/28/2025 | s.p. |
| inventor & applicant search in PE2E, patent data portal | 05/28/2025 | s.p. |
| invention & claims search in stn, PE2E | 05/28/2025 | s.p. |
| a61k31/519,5377; a61p5/06,08; a61p35/00 | 09/03/2025 | s.p. |
| inventor & applicant search in PE2E, patent data portal | 09/03/2025 | s.p. |
| invention & claims search in stnext, PE2E (incl. similarity search | 09/03/2025 | s.p. |

| /SARAH PIHONAK/<br>Primary Examiner, Art Unit 1627 | |
|---|---|

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
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| | 19/043,275 | HOWERTON et al. |
| | Examiner | Art Unit |
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| Interference Search | | | |
|---|---|---|---|
| US Class/CPC Symbol | US Subclass/CPC Group | Date | Examiner |
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| /SARAH PIHONAK/<br>Primary Examiner, Art Unit 1627 | |

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|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 1 | of | 21 | Attorney Docket Number | 50535-710.304 |

**U. S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 09/03/2025 |

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| | | | | Examiner Name | PIHONAK, SARAH |
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| | | | | Examiner Name | PIHONAK, SARAH |
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|---|---|
| Application Number | 19/043,275 |
| Filing Date | 01-31-2025 |
| First Named Inventor | HOWERTON; Alexis |
| Art Unit | 1627 |
| Examiner Name | PIHONAK, SARAH |
| Attorney Docket Number | 50535-710.304 |

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| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 09/03/2025 |
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| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 5 | of | 21 | Attorney Docket Number | 50535-710.304 |

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| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 6 | of | 21 | Attorney Docket Number | 50535-710.304 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
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| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 7 | of | 21 | Attorney Docket Number | 50535-710.304 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
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|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 14 | of | 21 | Attorney Docket Number | 50535-710.304 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 070 | STIKKELBROECK, Nike M. M. L. et al. High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and Leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 86(12):5721-5728 (2001). | ☐ |
| | 071 | STIKKELBROECK, Nike M. M. L. et. al. Monitoring of menstrual cycles, ovulation, and adrenal suppression by saliva sampling in female patients with 21- hydroxylase deficiency. Fertility & sterility 80(4):1030-1036 (2003). | ☐ |
| | 072 | THAKRAL, Naveen K. et al. Salt Disproportionation in the Solid State: Role of Solubility and Counterion Volatility. Molecular pharmaceutics 13(12):4141-4151 (2016). | ☐ |
| | 073 | The Journal of Clinical Endocrinology and Metabolism Author Guidelines. Oxford Academic (2025); [retrieved on 2025-06-09]. Available at URL: https://academic.oup.com/jcem/pages/author_guidelines. | ☐ |
| | 074 | TRAPP et al. Congenital adrenal hyperplasia: an update in children. Curr Opin Endocrinol Diabetes Obes. 18(3):166-70 (2011). | ☐ |
| | 075 | TURCU, Adina F. and Richard J. Auchus. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinology and Metabolism Clinics 44(2):275-296 (2015). | ☐ |
| | 076 | TURCU, Adina F., and Richard J. Auchus. Novel treatment strategies in congenital adrenal hyperplasia. Current Opinion in Endocrinology, Diabetes and Obesity 23(3):225-232 (2016). | ☐ |
| | 077 | TURCU, Adina F. et al. Single-dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. The Journal of Clinical Endocrinology and Metabolism 101(3):1174-1180 (2016). | ☐ |

**EXAMINER SIGNATURE**

| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 09/03/2025 |
|---|---|---|---|

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| | 078 | TURCU, Adina F. et al. Supplemental Information: Single-dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. The Journal of Clinical Endocrinology and Metabolism 101(3):1174-1180 (2016). | ☐ |
| | 079 | U.S. Provisional Application No. 62/822,815 filed on March 23, 2019. | ☐ |
| | 080 | U.S. Serial No. 17/586,228 Office Action dated June 10, 2022. | ☐ |
| | 081 | U.S. Serial No. 13/063,226 Office Action dated January 24, 2013. | ☐ |
| | 082 | U.S. Serial No. 16/388,620 Office Action dated July 15, 2019. | ☐ |
| | 083 | U.S. Serial No. 16/388,620 Office Action dated November 25, 2019. | ☐ |
| | 084 | U.S. Serial No. 16/639,540 Office Action dated July 11, 2022. | ☐ |
| | 085 | U.S. Serial No. 16/639,540 Office Action dated March 28, 2024. | ☐ |
| | 086 | U.S. Serial No. 16/639,540 Office Action dated May 25, 2023. | ☐ |
| | 087 | U.S. Serial No. 16/639,540 Office Action dated November 16, 2021. | ☐ |
| | 088 | U.S. Serial No. 16/639,540 Office Action dated September 28, 2023. | ☐ |
| | 089 | U.S. Serial No. 16/639,541 Office Action dated April 4, 2022. | ☐ |
| | 090 | U.S. Serial No. 17/063,592 Office Action dated December 7, 2021. | ☐ |

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| Sheet | 16 | of | 21 | Attorney Docket Number | 50535-710.304 |

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| | 091 | U.S. Serial No. 17/078,054 Office Action dated December 14, 2020. | ☐ |
| | 092 | U.S. Serial No. 17/359,411 Office Action dated January 6, 2022. | ☐ |
| | 093 | U.S. Serial No. 17/359,414 Office Action dated November 16, 2021. | ☐ |
| | 094 | U.S. Serial No. 17/586,228 Office Action dated March 30, 2022. | ☐ |
| | 095 | U.S. Serial No. 17/720,074 Office Action dated August 26, 2022. | ☐ |
| | 096 | U.S. Serial No. 18/078,649 Office Action dated March 21,2024. | ☐ |
| | 097 | U.S. Serial No. 18/078,649 Office Action dated October 9, 2024. | ☐ |
| | 098 | U.S. Serial No. 18/078,649 Office Action dated September 8, 2023. | ☐ |
| | 099 | U.S. Serial No. 18/307,718 Office Action dated October 12, 2023. | ☐ |
| | 100 | U.S. Serial No. 18/310,463 Office Action dated October 31, 2024. | ☐ |
| | 101 | U.S. Serial No. 19/043,264 Office Action dated April 25, 2025. | ☐ |
| | 102 | VARMA. Excipients used in the Formulation of Tablets. https://www.rroij.com/openaccess/excipients-used-in-the-formulationof-tablets-.php?aid=78260 Revised date: 26/07/2016. | ☐ |

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| | | | | Examiner Name | PIHONAK, SARAH |
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|---|---|---|---|
| | 103 | WALDRON, James. Spruce saws off only drug after 2nd hyperplasia fail, leaving biotech's direction in doubt. Fierce Biotech :1-2 (2024). | ☐ |
| | 104 | WANG, Zhu et al. Diagnosis of testicular adrenal rest tumors on ultrasound: a retrospective study of 15 cases report. Medicine 94(36):e1471, 1-6 (2015). | ☐ |
| | 105 | WILLIAMS, John P. Corticotropin-releasing factor 1 receptor antagonists: a patent review. Expert Opin Ther Pat 23(8):1057-68 (2013). | ☐ |
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| | 107 | YAMADA, Yasuki et al. New class of corticotropin-releasing factor (CRF) antagonists: small peptides having high binding affinity for CRF receptor. Journal of medicinal chemistry 47(5):1075-1078 (2004). | ☐ |
| | 108 | YASIR, Muhammad et al. Corticosteroid Adverse Effects. StatPearls, July 3, 2023; [retrieved on 2025-06-17]. Available at URL: https://www.ncbi.nlm.nih.gov/books/NBK531462/ pp. 1-14. | ☐ |
| | 109 | YU, Min Kyung et al. Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia. Annals of pediatric endocrinology and metabolism 20(3):155-161 (2015). | ☐ |
| | 110 | ZHANG et al. D-Level Essay in Statistics, 2009, How to Analyze Change from Baseline. Available at http://www.statistics.du.se/essays/D09 Zhang%20Ling%20&%20Han%20Kun.pdf (6/10/2009). | ☐ |
| | 111 | ZORRILLA, Eric P. et al., Progress in Corticotropin-Releasing Factor-1 Antagonist Development. Drug Discov Today 15(9-10):371-383 (2010). | ☐ |

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| | 112 | ZORRILLA, Eric P. et al. The therapeutic potential of CRF1 antagonists for anxiety. Expert opinion on investigational drugs 13(7):799-828 (2004). | ☐ |

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| Sheet | 19 | of | 21 | Attorney Docket Number | 50535-710.304 |

**TIMING STATEMENT**

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

**TIMING FEE**

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

**COPIES**

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

**SIZE FEE ASSERTION**

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☐ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☒ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

| Signature: | /Kaia R. Parenti/ | Date (YYYY-MM-DD) | 2025-08-13 |
|---|---|---|---|
| Name/Print | Kaia R. Parenti | Registration Number | 81050 |

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| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 20 | of | 21 | Attorney Docket Number | 50535-710.304 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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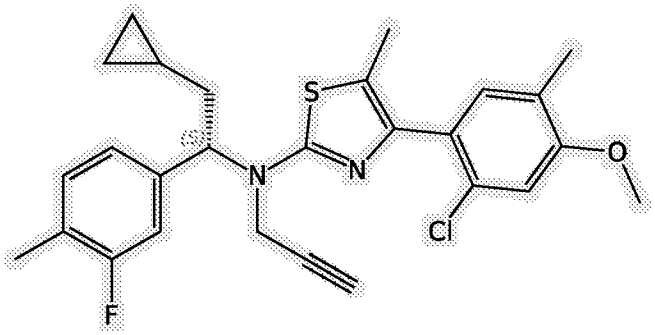
low-rate 72s schedule in rat)
IT 752253-39-7, SSR 125543
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(corticotropin-releasing factor 1 receptor antagonist, SSR125543 increased percentage of lever-presses occurring inter-response time bin, reducing total no. of responses in differential reinforcement of low-rate 72s schedule in rat)
RN 752253-39-7 CAPLUS
CN 2-Thiazolamine, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-2-propyn-1-yl- (CA INDEX NAME)




Absolute stereochemistry shown
Rotation (-)

OS.CITING REF COUNT: 34 THERE ARE 34 CAPLUS RECORDS THAT CITE THIS RECORD (34 CITINGS)
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 12:57:00 ON 03 SEP 2025)

FILE 'CAPLUS' ENTERED AT 12:57:59 ON 03 SEP 2025
L1 1 S US 20250177404/PN
E FASTING/CT
SET EXPAND CONTINUOUS
E E3+ALL/CT
L2 11096 S E16-E18
E "BIOAVAILABILITY"/CT
L3 67343 S E25
E "BIOABSORPTION"/CT
E E37+ALL/CT
L4 81806 S E48

FILE 'REGISTRY' ENTERED AT 13:01:22 ON 03 SEP 2025
L5 STRUCTURE UPLOADED
L6 50 S L5 SSS SAM

FILE 'CAPLUS' ENTERED AT 13:03:27 ON 03 SEP 2025
L7 19 S L6
L8 1 S L7 AND (L2 OR L3 OR L4)
L9 1 S L8 NOT L1
L10 0 S L7 AND (FOOD OR FED OR EAT? OR FAST OR FASTED OR FASTING)

FILE 'REGISTRY' ENTERED AT 13:04:50 ON 03 SEP 2025
L11 STRUCTURE UPLOADED
L12 32 S L11 SSS SAM
L13 565 S L11 SSS FULL

FILE 'CAPLUS' ENTERED AT 13:07:57 ON 03 SEP 2025

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L14          46 S L13
L15           1 S L14 AND (L2 OR L3 OR L4)
L16           2 S L14 AND (FOOD OR FED OR EAT? OR FAST OR FASTED OR FASTING)
L17           1 S (L15 OR L16) NOT L1

     FILE 'REGISTRY' ENTERED AT 13:08:58 ON 03 SEP 2025
                E SSR 126374/CN
L18           1 S E51

     FILE 'CAPLUS' ENTERED AT 13:09:17 ON 03 SEP 2025
L19           2 S L18
L20           1 S L19 AND (L2 OR L3 OR L4)
L21           1 S L19 AND (FOOD OR FED OR EAT? OR FAST OR FASTED OR FASTING)
L22           1 S L20 OR L21

     FILE 'REGISTRY' ENTERED AT 13:10:36 ON 03 SEP 2025
L23             STRUCTURE UPLOADED
L24           4 S L23 SSS SAM
L25          36 S L23 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:13:09 ON 03 SEP 2025
L26         217 S L25
L27           1 S L26 AND (L2 OR L3 OR L4)
L28          16 S L26 AND (FOOD OR FED OR EAT? OR FAST OR FASTED OR FASTING)
L29          16 S L27 OR L28
L30          15 S L29 NOT L1

     FILE 'REGISTRY' ENTERED AT 13:22:20 ON 03 SEP 2025
L31             STRUCTURE UPLOADED
L32           1 S L31 SSS SAM
L33           8 S L31 SSS FULL

     FILE 'CAPLUS' ENTERED AT 13:25:43 ON 03 SEP 2025
L34          61 S L33
L35           1 S L34 AND (L2 OR L3 OR L4)
L36           7 S L34 AND (FOOD OR FED OR EAT? OR FAST OR FASTED OR FASTING)
L37           7 S L35 OR L36
L38           6 S L37 NOT L1

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# PE2E SEARCH - Search History (Prior Art)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| L1 | 19 | ("10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220143037" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn. | (US-PGPUB; USPAT) | OR | ON | ON | 2025/05/16 04:02 PM |
| L2 | 390 | (a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND ((administer* OR administration* OR provid* OR deliver* OR treat*) WITH (fed OR fasted OR fasting OR food*)) | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/05/28 08:58 AM |
| L3 | 473 | (a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND ((endocrine OR hormone OR hormonal) WITH (disease* OR disorder* OR condition* OR syndrome*)) | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/05/28 09:10 AM |

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|---|---|---|---|---|---|---|---|
| L4 | 31 | ((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM. | (US-PGPUB; USPAT) | OR | ON | ON | 2025/05/28 09:26 AM |
| L5 | 21 | ((("HOWERTON") near3 ("Alexis"))).INV. | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/05/28 09:26 AM |
| L6 | 21 | ((("GERBER") near3 ("Hal"))).INV. | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/05/28 09:27 AM |
| L7 | 8 | (a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND ((endocrine OR hormone OR hormonal) WITH (disease* OR disorder* OR condition* OR syndrome*)) AND (L4 OR L5 OR L6) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/05/28 09:27 AM |
| L8 | 8 | (a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND (congenital adj4 adrenal adj4 hyperplasia) AND (L4 OR L5 OR L6) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/05/28 09:31 AM |
| L9 | 28 | (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND (congenital adj4 adrenal adj4 hyperplasia) AND (L4 OR L5 OR L6) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/05/28 09:31 AM |
| L10 | 4721 | (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND ((administer* OR administration* OR provid* OR deliver* OR treat*) WITH (fed OR fasted OR fasting OR food*)) | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/05/28 09:32 AM |
| L11 | 406 | (corticotropin adj8 releasing adj8 factor adj8 antagon*).ab,ti,clm. AND L10 | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, | OR | ON | ON | 2025/05/28 09:32 AM |

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|---|---|---|---|---|---|---|---|
| | | | IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | | | | |
| L12 | 54 | ("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR "20210361664" OR "20220133742" OR "20220143037" OR "20230159533" OR "20230321112" OR "20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177403" OR "20250195527" OR "8030304" OR "8563718" OR "10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220211711" OR "4328245" OR | (US-PGPUB; USPAT) | OR | ON | ON | 2025/08/28 02:19 PM |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn. | | | | | |
| L13 | 38 | L12 AND (food OR fed OR eat OR eaten OR meal OR ingest$3) | (US-PGPUB; USPAT) | OR | ON | ON | 2025/08/28 02:24 PM |
| L14 | 1 | "20250177404".pn. | (US-PGPUB) | OR | ON | ON | 2025/09/03 10:37 AM |
| L15 | 30 | (Artificial Intelligence) More like doc: US-20250177404-A1 Text: (JP-H0971528-A OR WO-2007109853-A1 OR BR-PI0717023-B8 OR US-20100203048-A1 OR CN-106102740-A OR TW-202400179-A OR EA-202090450-A1 OR US-20250177403-A1 OR US-20250195527-A1 OR EP-3784233-B1 OR HK-40040045-A OR US-20250177404-A1 OR HK-40040045-B OR AU-2023203095-A1 OR US-20240285593-A1 OR US-11304952-B2 OR US-11304950-B2 OR CA-3098562-A1 OR US-20220211711-A1 OR WO-2017087610-A1).did. | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/09/03 10:37 AM |
| L16 | 10 | L15 AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR suppress* OR decreas* OR reduc*)) AND ((administer* OR administrat* OR provid* OR given OR giving OR gave OR deliver*) adj15 (food OR eat OR fed OR fast$3)) | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/09/03 10:39 AM |
| L17 | 3923 | (a61k31/519,5377 OR a61p5/06,08 OR a61p35/00).cpc. AND | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, | OR | ON | ON | 2025/09/03 10:41 AM |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | (corticotropin adj12 releas* adj12 factor adj12 (antagon* OR inhibit* OR decreas* OR reduc*)) | CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | | | | |
| L18 | 774 | L17 AND ((administer* OR administrat* OR provid* OR given OR giving OR gave OR deliver*) adj15 (food OR eat OR fed OR fast$3)) | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/09/03 10:42 AM |
| L19 | 220 | ((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20180427")) AND L18 | (US-PGPUB; USPAT) | OR | ON | ON | 2025/09/03 11:08 AM |
| L20 | 54 | ("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR "20210361664" OR "20220133742" OR | (US-PGPUB; USPAT) | OR | ON | ON | 2025/09/03 11:34 AM |

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|---|---|---|---|---|---|---|---|
| | | "20220143037" OR "20230159533" OR "20230321112" OR "20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177403" OR "20250195527" OR "8030304" OR "8563718" OR "10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn. | | | | | |
| L21 | 33 | L20 AND ((administer* OR administrat* OR provid* OR given OR giving OR gave OR deliver*) adj15 (food OR eat OR fed OR fast$3)) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/09/03 11:37 AM |
| L22 | 35 | ((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM. | (US-PGPUB; USPAT) | OR | ON | ON | 2025/09/03 11:57 AM |
| L23 | 24 | ((("HOWERTON") near3 ("Alexis")) OR (("GERBER") near3 ("Hal"))).INV. | (US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT) | OR | ON | ON | 2025/09/03 11:57 AM |
| L24 | 32 | (L22 OR L23) AND (corticotropin adj12 releas* adj12 factor adj12 (antagon* OR inhibit* OR decreas* OR reduc*)) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/09/03 11:58 AM |
| L25 | 32 | L24 AND ((administer* OR administrat* OR provid* OR given OR giving OR gave OR deliver*) adj15 (food OR eat OR fed OR fast$3)) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/09/03 11:58 AM |
| L26 | 6 | ("11304950" OR | (USPAT) | OR | ON | ON | 2025/09/09 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | "11858932" OR "12098152" OR "11311549" OR "11344557" OR "11351177").pn. | | | | | 04:32 PM |

## PE2E SEARCH - Search History (Interference)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| N1 | 1038 | (a61k31/519,5377 OR a61p5/06,08 OR a61p35/00).cpc. AND (corticotropin adj12 releas* adj12 factor adj12 (antagon* OR inhibit* OR decreas* OR reduc*)) | (US-PGPUB; USPAT) | OR | ON | ON | 2025/09/03 11:55 AM |
| N2 | 245 | N1 AND ((administer* OR administrat* OR provid* OR given OR giving OR gave OR deliver*) adj15 (food OR eat OR fed OR fast$3)) | (US-PGPUB; USPAT) | OR | ON | ON | 2025/09/03 11:55 AM |

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | HOWERTON; Alexis et al. | Group Art Unit: | 1627 |
| Serial Number: | 19/043,275 | Examiner: | PIHONAK, SARAH |
| Filing or 371 (c) Date: | 2025-01-31 | **CONFIRMATION NO:** | **5486** |
| Title: | METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS | | |

**FILED ELECTRONICALLY ON: October 3, 2025**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $280.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: October 3, 2025

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 1 | of | 5 | Attorney Docket Number | 50535-710.304 |

**U. S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | None | | | |

**FOREIGN PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 2 | of | 5 | Attorney Docket Number | 50535-710.304 |

| **NON-PATENT LITERATURE DOCUMENTS** | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 001 | BRADLEY, D. Anawalt et al. Chapter 12: Testes. Greenspan's Basic & Clinical Endocrinology. 10th ed. New York: McGraw-Hill Education (pp. 413-442) (2018). | ☐ |
| | 002 | EP3784233 Case Details for ACT_34386/2025 (1 pg) (2025). | ☐ |
| | 003 | FDA Approves New Treatment for Congenital Adrenal Hyperplasia, US Food and Drug Administration, December 13, 2024. Available at URL: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-congenital-adrenal-hyperplasia? pp.1-2. | ☐ |
| | 004 | SPEISER, Phyllis W. et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism 103(11):4043-4088 (2018). | ☐ |
| | 005 | Spruce Power Holding Corporation. Quarterly Report (Form 10-Q) for the period ended June 30, 2024. United States Securities and Exchange Commission, August 13, 2024. Available at: https://www.sec.gov/Archives/edgar/data/1772720/000162828024037238/spru-20240630.htm pp. 1-53. | ☐ |
| | 006 | U.S. Serial No. 19/043,264 Office Action dated August 18, 2025. | ☐ |
| | 007 | U.S. Serial No. 19/043,303 Office Action dated September 5, 2025. | ☐ |
| | 008 | World Health Organization. Drug Information 33(1):122 (2019). | ☐ |

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| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 3 | of | 5 | Attorney Docket Number | 50535-710.304 |

**TIMING STATEMENT**

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

**TIMING FEE**

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

**COPIES**

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

**SIZE FEE ASSERTION**

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

| Signature: | /Kaia R. Parenti/ | Date (YYYY-MM-DD) | 2025-10-03 |
|---|---|---|---|
| Name/Print | Kaia R. Parenti | Registration Number | 81050 |

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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| Sheet | 4 | of | 5 | Attorney Docket Number | 50535-710.304 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | HOWERTON; Alexis et al. | Group Art Unit: | 1627 |
| Serial Number: | 19/043,275 | Examiner: | PIHONAK, SARAH |
| Filing or 371 (c) Date: | 2025-01-31 | **CONFIRMATION NO:** | **5486** |
| Title: | METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS | | |

**FILED ELECTRONICALLY ON: October 3, 2025**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $280.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: October 3, 2025

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

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| | | | | Filing Date | 01-31-2025 |
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| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 1 | of | 5 | Attorney Docket Number | 50535-710.304 |

**U. S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | None | | | |

**FOREIGN PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

| EXAMINER SIGNATURE | | | |
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|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 001 | BRADLEY, D. Anawalt et al. Chapter 12: Testes. Greenspan's Basic & Clinical Endocrinology. 10th ed. New York: McGraw-Hill Education (pp. 413-442) (2018). | ☐ |
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| | 004 | SPEISER, Phyllis W. et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism 103(11):4043-4088 (2018). | ☐ |
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## TIMING FEE

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## COPIES

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☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

| Signature: | /Kaia R. Parenti/ | Date (YYYY-MM-DD) | 2025-10-03 |
|---|---|---|---|
| Name/Print | Kaia R. Parenti | Registration Number | 81050 |

PTO/SB/08 (01-25)
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| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 4 | of | 5 | Attorney Docket Number | 50535-710.304 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **10/03/2025 04:01:57 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | JENNIFER VAIL |
| PATENT CENTER # | 72579405 | FILING DATE | 01/31/2025 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Kaia Parenti |

## Documents

**TOTAL DOCUMENTS: 11**

| DOCUMENT | | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|---|
| Spruce_50535-710-304_sIDS.pdf | | 9 | - | 291 KB |
| Spruce_50535-710-304_sIDS-TRAN.LET.pdf | (1-4) | 4 | Transmittal Letter | 155 KB |
| Spruce_50535-710-304_sIDS-IDS.pdf | (5-9) | 5 | Information Disclosure Statement (IDS) Form (SB08) | 131 KB |
| NPL_EP3784233_CaseDetails_2025.pdf | | 1 | Non Patent Literature | 66 KB |
| NPL_US19043275_OA_2025_09_12.pdf | | 8 | Non Patent Literature | 223 KB |
| NPL_US19043303_OA_2025_09_05.pdf | | 11 | Non Patent Literature | 346 KB |

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|---|---|---|---|
| NPL_US19043264_OA_2025_08_18.pdf | 14 | Non Patent Literature | 469 KB |
| NPL_World_Drug_Information_122_2019.pdf | 1 | Non Patent Literature | 499 KB |
| NPL_FDA_Congenital_Adrenal_Hyperplasia_2024.pdf | 2 | Non Patent Literature | 760 KB |
| NPL_Bradley_Chapter_12_Testes_413-442.pdf | 55 | Non Patent Literature | 1508 KB |
| NPL_Spruce_Quarterly_Report_2024.pdf | 53 | Non Patent Literature | 16322 KB |
| NPL_SPEISER_Congenital_adrenal_4043_4088.pdf | 46 | Non Patent Literature | 22285 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| Spruce_50535-710-304_sIDS.pdf | CBABE8CB0E13E43BA3B898F28A2CB51BE0431863C9BEFCCEF9268334E4300488584523CE6F12991C57EE5836CAFAE343019FA8001AE310E6B6AB423F3FA44A7A |
| Spruce_50535-710-304_sIDS-TRAN.LET.pdf | 4F312C692BA5753AB530F7A99D25CAF2D8AA53D4D6A451EF5FA5A94BD82BD982659988BDCA5259010A3D5FB65E96652B84B8904FE3CF2E24618F222F51111521 |
| Spruce_50535-710-304_sIDS-IDS.pdf | F557A1806D5F557EFA40A7D8226B3EE431332DCE13E3D1D88403288C2774A585E1449C6B77E90A3728ECDB51DA257F24420811B6FF6D3CA3266BDCC3393A9E18 |
| NPL_EP3784233_CaseDetails_2025.pdf | 70063DBDF2F84600EEBC1D9CEB6FE8D1FA040310AD01AFB19DD9440BB42522E3B58173AF3AA799465C60E5C471C6E6D9A58AD131AA6249E8C77DBD6474DC7EB3 |
| NPL_US19043275_OA_2025_09_12.pdf | 21D866E3EFAF37A824C57B8595681E883A50923FFF78950F4B2B781EFB460B705A1F0C2F2B7C543EE5B73B51F402EE843CD83883614702C044526B889C6350A6 |
| NPL_US19043303_OA_2025_09_05.pdf | FFB5FE03CB9CE3086C759B5704177AFA34D6C5290651E66249F61466EAA2E7F33764FAA97890DEBA78AC38D31C40CA8EADA4AB20C0840EE9C904B33E32AF117A |
| NPL_US19043264_OA_2025_08_18.pdf | 1C54AA0B10A4C834A633A60D417CC25C7073B99D8C9FE37EA4D1DA71697E01434EF3AE196AFE05B2C522418BC24C03239A44C5793EA98E9278D02D747D9492E3 |
| NPL_World_Drug_Information_122_2019.pdf | 23A0BCEBA3BFA82F6F91CB62B53116EF15438B475A111385E24219A8C7C87B0FE80E25CA833844AE8212CB221F6196AA36 |

| | |
|---|---|
| | B9782E2CD8EF82889DD04DB9C9A055 |
| NPL_FDA_Congenital_Adrenal_Hyperplasia_2024.pdf | 8010561785130E9DB463761F495158C13AF22035FC8EC019F7B8580D1E6763B4A47D0E0EAFC5DB796A7DA05312E3A0AAA94F495AA75B1B046EB4BEFC146F8998 |
| NPL_Bradley_Chapter_12_Testes_413-442.pdf | 464025D9AC0F21E0D06D0767BF8C470BB0DAF976E048D3A87D8DD7A55CEA44C22B5C57D660C670754EF7D97B81BC911BF01CF1B3B10EA60B0814F42C0392FEAE |
| NPL_Spruce_Quarterly_Report_2024.pdf | CD93E8C17AA4157421D317D10B340427073D4B8619F011C221455D4298240F8C81D40B2CC573059A3B8FB2ED5CB63F832F7F7EB1606051446F85B0934739ED27 |
| NPL_SPEISER_Congenital_adrenal_4043_4088.pdf | 7C3A435DC5BED745595FB6B78845BB38694684F0AEEFE1FA32DE9EBB303C94D13D72CCE742D8008AC544E0B2D29D3476D2786141CA7017FEF59C003DE2432E20 |

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**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **10/03/2025 04:01:57 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | JENNIFER VAIL |
| PATENT CENTER # | 72579405 | AUTHORIZED BY | Kaia Parenti |
| CUSTOMER # | 21971 | FILING DATE | 01/31/2025 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | Alexis HOWERTON |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| **DA / 232415** | **E202503G02546132** | **JENNIFER VAIL** |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1806 | SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT | 280.00 | 1 | 280.00 |
| | | | **TOTAL AMOUNT:** | **¤280.00** |

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PTO/AIA/01 (06-12)
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# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

| Title of Invention | METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS |
|---|---|

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 18/941,832 filed on November 8, 2024.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

## WARNING:

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LEGAL NAME OF INVENTOR

Inventor: Hal GERBER Date (Optional) :

Signed by:
Signature: 5EBA0FD238B74B1...

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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Docusign Envelope ID: FD12DDB0-FA13-4E3F-939F-AFDBB022F6BC

PTO/AIA/01 (06-12)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

| Title of Invention | METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS |
|---|---|

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 18/941,832 filed on November 8, 2024.

The above-identified application was made or authorized to be made by me.

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LEGAL NAME OF INVENTOR

Inventor: Alexis HOWERTON Date (Optional) :

Signed by:
Signature: Alexis Howerton
1CA8774213A140D...

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0032. Public burden for this form is estimated to average 1 minute per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.** If filing this completed form by mail, send to: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **11/20/2025 03:37:19 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | Colleen Mensching |
| PATENT CENTER # | 73268881 | FILING DATE | 01/31/2025 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Kaia Parenti |

## Documents

## TOTAL DOCUMENTS: 2

| DOCUMENT | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|
| Declaration_Alexis_HOWERTON_Spruce_50535-710.303.pdf | 2 | Oath or Declaration filed | 361 KB |

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| Declaration_Hal_GERBER_Spruce_50535-710.303.pdf | 2 | Oath or Declaration filed | 358 KB |

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## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| Declaration_Alexis_HOWERTON_Spruce_50535-710.303.pdf | 8DDDAB7F3B3A3047C5D60B6381668D9F62098E25156F8890771EA228925246DFCABDCD1255E601BB339381B41FFC88F861DFF46BCCE9395540E7E1774B72303A |
| Declaration_Hal_GERBER_Spruce_50535-710.303.pdf | EFB3648A1FEB23BC8C055AFC2FC3DA23CD9D7CB16F3BA7AE9889034B3F5E35E40A0205C4D3F16B79818A924337CEE9E603E6495E65F30882AFF284338438D659 |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>19/043,275 | Filing Date<br>01/31/2025 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY:** ☑ LARGE ☐ SMALL ☐ MICRO

## APPLICATION AS FILED - PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | | RATE ($) | FEE ($) |
|---|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | | x $200 = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | | x $ 600 = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | | TOTAL | |

## APPLICATION AS AMENDED - PART II

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | 11/21/2025 | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total (37 CFR 1.16(i)) | * 19 | Minus | ** 21 | = 0 | | x $200 = | 0 |
| | Independent (37 CFR 1.16(h)) | * 1 | Minus | *** 3 | = 0 | | x $ 600 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | 0 |

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total (37 CFR 1.16(i)) | * | Minus | ** | = | | x $ 0 = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | | x $ 0 = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | |

| | |
|---|---|
| * If the entry in column 1 is less than the entry in column 2, write "0" in column 3. | LIE |
| ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". | /DEBORAH A POLLARD/ |
| *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". | |
| The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1. | |

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | HOWERTON; Alexis et al. | Group Art Unit: | 1627 |
| Serial Number: | 19/043,275 | Examiner: | PIHONAK, SARAH |
| Filing or 371 (c) Date: | 2025-01-31 | **CONFIRMATION NO:** | **5486** |
| Title: | METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS | | |

**FILED ELECTRONICALLY ON: November 24, 2025**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: November 24, 2025

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

PTO/SB/08 (01-25)
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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 1 | of | 8 | Attorney Docket Number | 50535-710.304 |

**U. S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | 001 | US-6586456 | 07-01-2003 | FONTAINE; Evelyne et al. | |

**FOREIGN PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 2 | of | 8 | Attorney Docket Number | 50535-710.304 |

| **NON-PATENT LITERATURE DOCUMENTS** | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 001 | ÇAKIR et al., Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia. J Clin Res Pediatr Endocrinol 4(2):94-100 (2012). | ☐ |
| | 002 | ANAWALT, Bradley D. et al. Chapter 12: Testes. Extract from Textbook: Gardner & Shoback, Greenspan's Basic & Clinical Endocrinology, 10th ed. (McGraw-Hill Education), pps. 413, 440-441 (2018). | ☐ |
| | 003 | BACON et al., Effect of Cortisol Treatment on Hormonal Relationships in Congenital Adrenal Hyperplasia. Clinical Endocrinology 6:113-126 (1977). | ☐ |
| | 004 | BENVENGA et al., Testicular adrenal rests: evidence for luteinizing hormone receptors and for distinct types of testicular nodules differing for their autonomization. European Journal of Endocrinology 141:231-237 (1999). | ☐ |
| | 005 | BHATT, Deepak L. et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. N Engl J Med 370(15):1393-401 (2014). | ☐ |
| | 006 | BROWN, Marie T. et al. Medication Adherence: WHO Cares? Mayo Clin Proc 86(4):304-314 (2011). | ☐ |
| | 007 | Chemical Abstracts Service. CAS Registry: 752253-39-7. 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-((1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-2-propyn-1-yl-2-thiazolamine: pp. 1-35. STN Entry Date October 11, 2005. Retrieved October 14, 2025. Retrieved from :https://pubchem.ncbi.nlm.nih.gov/compound/5282340. | ☐ |
| | 008 | CLAAHSEN et al., Testicular Tumors in Patients with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency Show Functional Features of Adrenocortical Tissue. J Clin Endocrinol Metab. 92(9):3674-80 (2007). | ☐ |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 3 | of | 8 | Attorney Docket Number | 50535-710.304 |

| **NON-PATENT LITERATURE DOCUMENTS** | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 009 | Clinical Study Protocol SPR001-201. A Phase 2, Multiple-Dose, Dose-Escalation Study to Evaluate the Safety and Efficacy of SPR001 in Adults with Classic Congenital Adrenal Hyperplasia (CAH). (8/23/2018). | ☐ |
| | 010 | Declaration of Associate Professor Dr Henrik Falhammar dated November 14, 2025. | ☐ |
| | 011 | Declaration of Professor Peter Hindmarsh dated October 23, 2025. | ☐ |
| | 012 | Declaration of Vivian H. Lin, M.D. dated November 14, 2025. | ☐ |
| | 013 | FEDOROVA, Olga et al. What is the need for adrenalectomy in patients with congenital adrenal hyperplasia in the era of CRF1/ACT inhibitors? Frontiers in Endocrinology (Lausanne) 16:1693063, 1-10 (2025). | ☐ |
| | 014 | GUPTA et al., Corticosteroid Physiology and Principles of Therapy. Indian J Pediatr 75(10):1039-1044 (2008). | ☐ |
| | 015 | GWATHMEY et al., Glucocorticoid-Induced Fetal Programming Alters the Functional Complement of Angiotensin Receptor Subtypes Within the Kidney. Hypertension 57(3):620-6 (2011). | ☐ |
| | 016 | Henrik Falhammar, M.D., Ph.D., FRACP, Curriculum Vitae (No date available). | ☐ |
| | 017 | HINDMARSH et al., Congenital Adrenal Hyperplasia A Comprehensive Guide. Elsevier, ISBN: 978-0-12-811483-4 (pp. 263-264 and 319-320) (2017). | ☐ |
| | 018 | MATSUBARA. Pathophysiological Role of Angiotensin II Type 2 Receptor in Cardiovascular and Renal Diseases. Circ Res. 83:1182-1191 (1998). | ☐ |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 4 | of | 8 | Attorney Docket Number | 50535-710.304 |

| **NON-PATENT LITERATURE DOCUMENTS** | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 019 | MEENA, H. et al., Growth Pattern and Clinical Profile of Indian Children with Classical 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia on Treatment. Indian J Pediatr. 86(6):496-502 (2019). | ☐ |
| | 020 | MESA et al., Immunophenotypic differences between neoplastic and non-neoplastic androgen-producing cells containing and lacking Reinke crystals. Virchows Arch. 469(6):679-686 (2016). | ☐ |
| | 021 | MORRIS, David. Steroid-induced Diabetes and Hyperglycaemia. Part 1: Mechanisms and Risks. Diabetes & Primary Care 20(4):151-153 (2018). | ☐ |
| | 022 | NAGURNEY et al., The Accuracy and completeness of Data Collected by Prospective and Retrospective Methods. ACAD EMERG MED 12(9):884-95 (September 2005). | ☐ |
| | 023 | Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Denying Institution of Inter Partes Review in U.S. Patent No. 12,115,166 dated October 03, 2025 (pp 1-3) (PGR-2025-00032). | ☐ |
| | 024 | NEWFIELD, Ron S. et al. Crinecerfont, a CRF1 Receptor Antagonist, Lowers Adrenal Androgens in Adolescents with Congenital Adrenal Hyperplasia. The Journal of Clinical Endocrinology & Metabolism 108(11):2871-2878 (2023). | ☐ |
| | 025 | POYRAZOGLU et al., Prevalence of testicular microlithiasis in males with congenital adrenal hyperplasia and its association with testicular adrenal rest tumors. Horm Res Paediatr. 73:443-448 (2010). | ☐ |
| | 026 | Regulation (EC) No 141/2000 Of the European Parliament and of the Council of 16 December 1999 on orphan medical products (pp. 1-5). | ☐ |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

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| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 5 | of | 8 | Attorney Docket Number | 50535-710.304 |

| **NON-PATENT LITERATURE DOCUMENTS** | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 027 | SOWERS et al., Effect of dexamethasone on gonadotropin responsiveness to luteinizing hormone-releasing hormone and clomiphene in women with secondary amenorrhea. Am J Obstet Gynecol. 134(3):325-8 (1979 Jun 1). | ☐ |
| | 028 | SPIERLING, Samantha R, and Eric P Zorrilla. et al. Don't stress about CRF: Assessing the translational failures of CRF1 antagonists. Psychopharmacology 234(9-10):1467-1481 (2017). | ☐ |
| | 029 | U.S. Serial No. 17/578,149 Office Action dated October 6, 2025. | ☐ |
| | 030 | U.S. Serial No. 18/438,060 Office Action dated October 7, 2025. | ☐ |
| | 031 | Vivian H. Lin, Curriculum Vitae (No date available). | ☐ |
| | 032 | XAVIER et al., Gene Expression Control by Glucocorticoid Receptors during Innate Immune Responses. Front. Endocrinol. 7:31 (2016). | ☐ |
| | 033 | XUE et al. Glucocorticoid Modulates Angiotensin II Receptor Expression Patterns and Protects the Heart from Ischemia and Reperfusion Injury. PLoS One 9(9):e106827 (2014). | ☐ |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 6 | of | 8 | Attorney Docket Number | 50535-710.304 |

**TIMING STATEMENT**

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

**TIMING FEE**

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

**COPIES**

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

**SIZE FEE ASSERTION**

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

| Signature: | /Victoria Cheng/ | Date (YYYY-MM-DD) | 2025-11-24 |
|---|---|---|---|
| Name/Print | Victoria Cheng | Registration Number | 79641 |

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
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| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 7 | of | 8 | Attorney Docket Number | 50535-710.304 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | HOWERTON; Alexis et al. | Group Art Unit: | 1627 |
| Serial Number: | 19/043,275 | Examiner: | PIHONAK, SARAH |
| Filing or 371 (c) Date: | 2025-01-31 | **CONFIRMATION NO:** | **5486** |
| Title: | METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS | | |

**FILED ELECTRONICALLY ON: November 24, 2025**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: November 24, 2025

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
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| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 1 | of | 8 | Attorney Docket Number | 50535-710.304 |

**U. S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | 001 | US-6586456 | 07-01-2003 | FONTAINE; Evelyne et al. | |

**FOREIGN PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 2 | of | 8 | Attorney Docket Number | 50535-710.304 |

| **NON-PATENT LITERATURE DOCUMENTS** | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 001 | ÇAKIR et al., Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia. J Clin Res Pediatr Endocrinol 4(2):94-100 (2012). | ☐ |
| | 002 | ANAWALT, Bradley D. et al. Chapter 12: Testes. Extract from Textbook: Gardner & Shoback, Greenspan's Basic & Clinical Endocrinology, 10th ed. (McGraw-Hill Education), pps. 413, 440-441 (2018). | ☐ |
| | 003 | BACON et al., Effect of Cortisol Treatment on Hormonal Relationships in Congenital Adrenal Hyperplasia. Clinical Endocrinology 6:113-126 (1977). | ☐ |
| | 004 | BENVENGA et al., Testicular adrenal rests: evidence for luteinizing hormone receptors and for distinct types of testicular nodules differing for their autonomization. European Journal of Endocrinology 141:231-237 (1999). | ☐ |
| | 005 | BHATT, Deepak L. et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. N Engl J Med 370(15):1393-401 (2014). | ☐ |
| | 006 | BROWN, Marie T. et al. Medication Adherence: WHO Cares? Mayo Clin Proc 86(4):304-314 (2011). | ☐ |
| | 007 | Chemical Abstracts Service. CAS Registry: 752253-39-7. 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-((1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-2-propyn-1-yl-2-thiazolamine: pp. 1-35. STN Entry Date October 11, 2005. Retrieved October 14, 2025. Retrieved from :https://pubchem.ncbi.nlm.nih.gov/compound/5282340. | ☐ |
| | 008 | CLAAHSEN et al., Testicular Tumors in Patients with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency Show Functional Features of Adrenocortical Tissue. J Clin Endocrinol Metab. 92(9):3674-80 (2007). | ☐ |

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| Sheet | 3 | of | 8 | Attorney Docket Number | 50535-710.304 |

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| | 009 | Clinical Study Protocol SPR001-201. A Phase 2, Multiple-Dose, Dose-Escalation Study to Evaluate the Safety and Efficacy of SPR001 in Adults with Classic Congenital Adrenal Hyperplasia (CAH). (8/23/2018). | ☐ |
| | 010 | Declaration of Associate Professor Dr Henrik Falhammar dated November 14, 2025. | ☐ |
| | 011 | Declaration of Professor Peter Hindmarsh dated October 23, 2025. | ☐ |
| | 012 | Declaration of Vivian H. Lin, M.D. dated November 14, 2025. | ☐ |
| | 013 | FEDOROVA, Olga et al. What is the need for adrenalectomy in patients with congenital adrenal hyperplasia in the era of CRF1/ACT inhibitors? Frontiers in Endocrinology (Lausanne) 16:1693063, 1-10 (2025). | ☐ |
| | 014 | GUPTA et al., Corticosteroid Physiology and Principles of Therapy. Indian J Pediatr 75(10):1039-1044 (2008). | ☐ |
| | 015 | GWATHMEY et al., Glucocorticoid-Induced Fetal Programming Alters the Functional Complement of Angiotensin Receptor Subtypes Within the Kidney. Hypertension 57(3):620-6 (2011). | ☐ |
| | 016 | Henrik Falhammar, M.D., Ph.D., FRACP, Curriculum Vitae (No date available). | ☐ |
| | 017 | HINDMARSH et al., Congenital Adrenal Hyperplasia A Comprehensive Guide. Elsevier, ISBN: 978-0-12-811483-4 (pp. 263-264 and 319-320) (2017). | ☐ |
| | 018 | MATSUBARA. Pathophysiological Role of Angiotensin II Type 2 Receptor in Cardiovascular and Renal Diseases. Circ Res. 83:1182-1191 (1998). | ☐ |

| **EXAMINER SIGNATURE** | | | |
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| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 4 | of | 8 | Attorney Docket Number | 50535-710.304 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 019 | MEENA, H. et al., Growth Pattern and Clinical Profile of Indian Children with Classical 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia on Treatment. Indian J Pediatr. 86(6):496-502 (2019). | ☐ |
| | 020 | MESA et al., Immunophenotypic differences between neoplastic and non-neoplastic androgen-producing cells containing and lacking Reinke crystals. Virchows Arch. 469(6):679-686 (2016). | ☐ |
| | 021 | MORRIS, David. Steroid-induced Diabetes and Hyperglycaemia. Part 1: Mechanisms and Risks. Diabetes & Primary Care 20(4):151-153 (2018). | ☐ |
| | 022 | NAGURNEY et al., The Accuracy and completeness of Data Collected by Prospective and Retrospective Methods. ACAD EMERG MED 12(9):884-95 (September 2005). | ☐ |
| | 023 | Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Denying Institution of Inter Partes Review in U.S. Patent No. 12,115,166 dated October 03, 2025 (pp 1-3) (PGR-2025-00032). | ☐ |
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|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 5 | of | 8 | Attorney Docket Number | 50535-710.304 |

| **NON-PATENT LITERATURE DOCUMENTS** | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 027 | SOWERS et al., Effect of dexamethasone on gonadotropin responsiveness to luteinizing hormone-releasing hormone and clomiphene in women with secondary amenorrhea. Am J Obstet Gynecol. 134(3):325-8 (1979 Jun 1). | ☐ |
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| | 033 | XUE et al. Glucocorticoid Modulates Angiotensin II Receptor Expression Patterns and Protects the Heart from Ischemia and Reperfusion Injury. PLoS One 9(9):e106827 (2014). | ☐ |

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| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 6 | of | 8 | Attorney Docket Number | 50535-710.304 |

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Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached timing statement under 37 CFR 1.97(e).

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☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

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| Signature: | /Victoria Cheng/ | Date (YYYY-MM-DD) | 2025-11-24 |
|---|---|---|---|
| Name/Print | Victoria Cheng | Registration Number | 79641 |

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| Sheet | 7 | of | 8 | Attorney Docket Number | 50535-710.304 |

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|---|---|---|
| **19/043,275** | **11/24/2025 04:27:36 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | JENNIFER VAIL |
| PATENT CENTER # | 73316832 | AUTHORIZED BY | Victoria Cheng |
| CUSTOMER # | 21971 | FILING DATE | 01/31/2025 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | Alexis HOWERTON |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
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| **DA / 232415** | **E2025ANG28096114** | **JENNIFER VAIL** |

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| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Victoria Cheng |

## Documents

**TOTAL DOCUMENTS: 35**

| DOCUMENT | | PAGES | DESCRIPTION | SIZE (KB) |
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| Spruce 50535-710_304_IDS-TRAN.LET.pdf | (1-4) | 4 | Transmittal Letter | 145 KB |
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| NPL_029_SPIERLING_CRF_Assessings_1467_1481_2017.pdf | 35A51E8914AA1A2BD3CBA3385DFC54E3B802ADC5A096B51DC70B81029DBC4B8CB4326851CAD7394D646E711D044A0DBB7B8417074699FBFED5FA039CD8D5148D |
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the

International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

**PATENT**
**Attorney Docket No. 50535-710.304**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re the Application of:<br><br>Inventors: Alexis Howerton et al.<br><br>Application No.: 19/043,275<br><br>Filing Date: January 31, 2025<br><br>Title: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS | Confirmation No.: 5486<br><br>Art Unit: 1627<br><br>Examiner: Pihonak, Sarah<br><br>Customer No.: 21971<br><br>Certificate of Electronic Filing<br>I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office's electronic filing system to the USPTO on November 24, 2025.<br><br>By: / Colleen Mensching /<br>Colleen Mensching |

Mailstop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION**

Dear Commissioner:

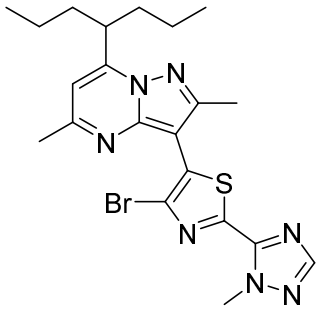
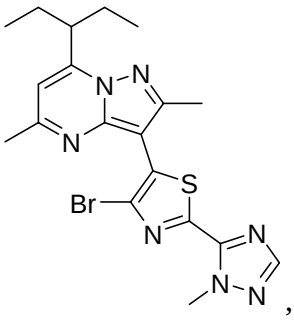
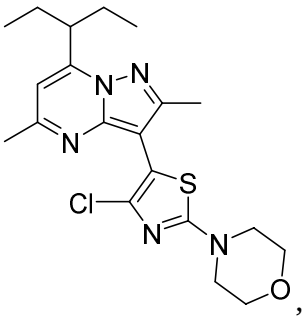
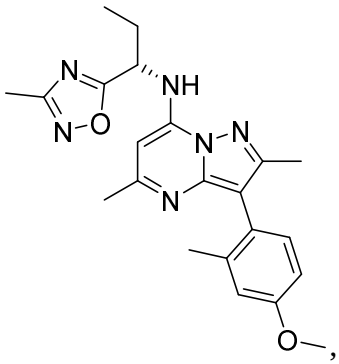
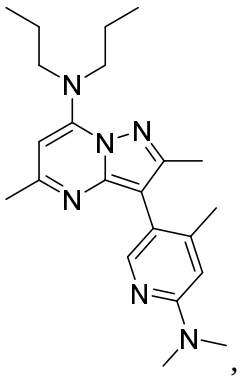
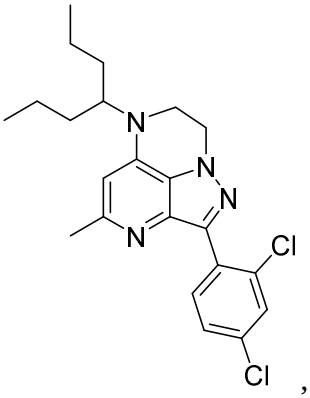
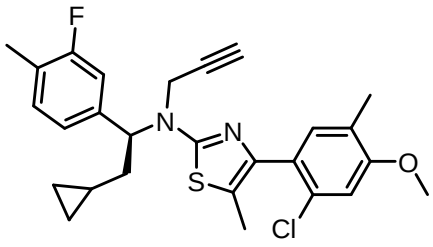
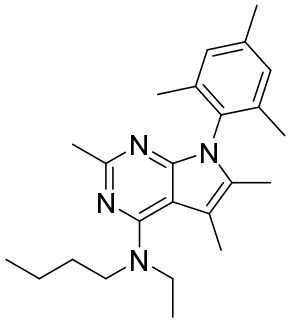
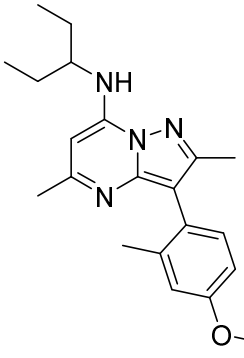
In response to the Non-Final Office Action mailed September 12, 2025, setting an initial due date of December 12, 2025, Applicant respectfully requests reconsideration of the above-referenced application in view of the following amendments and remarks.

**Amendments to the Claims** begin on page **2** of this paper.
**Remarks** begin on page **5** of this paper.
**Conclusion** begins on page **6** of this paper.

## AMENDMENTS TO THE CLAIMS

### Listing of the Claims

1. (**Currently Amended**) A method of treating an endocrine disorder associated with corticotropin-releasing factor type-1 ($CRF_1$) activity, comprising administering to a subject in need thereof a small molecule $CRF_1$ antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule $CRF_1$ antagonist is:

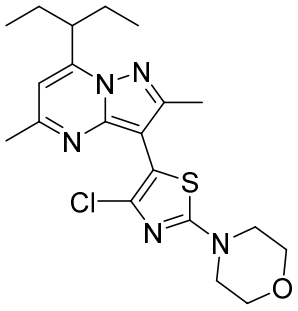
,
,
,
,
,
, SSR-126374,
,
, or
, or a pharmaceutically acceptable salt thereof,

wherein the small molecule $CRF_1$ antagonist is administered to the subject twice per day, and

wherein the subject is in the fed state,

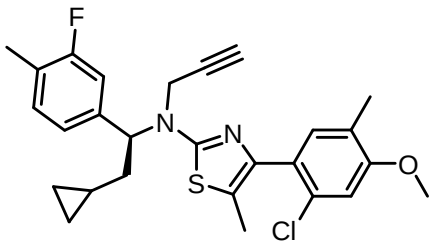
wherein the endocrine disorder associated with $CRF_1$ activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).

2. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is:




, or a pharmaceutically acceptable salt thereof.

3. (Previously Presented) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is:




, or a pharmaceutically acceptable salt thereof.

4. (Canceled)
5. (Original) The method of claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).
6. (Original) The method of claim 1, wherein the subject is receiving a glucocorticoid in conjunction with the administering of the small molecule $CRF_1$ antagonist.
7. (Original) The method of claim 6, wherein the glucocorticoid comprises beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone, or a combination thereof.
8. (Original) The method of claim 7, wherein the glucocorticoid is hydrocortisone.
9. (Original) The method of claim 1, wherein the subject is an adolescent.
10. (Original) The method of claim 1, wherein the subject is at least 18 years old.

11. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.
12. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 50 mg.
13. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 100 mg.
14. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 200 mg.
15. (Original) The method of claim 11, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 400 mg.
16. (Cancelled)
17. (Cancelled)
18. (Cancelled)
19. (Cancelled)
20. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered orally.
21. (Original) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is formulated as a capsule or tablet.
22. (Previously Presented) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered less than about 6 hours before sleep.
23. (Previously Presented) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered less than about 3 hours before sleep.
24. (Previously Presented) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered in the evening.

## REMARKS

Claims 1-15 and 20-24 were pending prior to entry of the amendments presented in this response. Claim 1 has been amended herein to incorporate the subject matter of dependent claim 4. As such, claim 4 is canceled herein. No new matter is believed to be added by way of the amendment made herein. Accordingly, upon entry of the proposed amendments, claims 1-3, 5-15, and 20-24 will be under examination.

### Allowable Subject Matter

Claims 3 and 4 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Without conceding to the basis of any rejections made in the Office Action, and for the purpose of compact prosecution, Applicant amends claim 1 to incorporate the subject matter of dependent claim 4. Accordingly, Applicant respectfully submits amended claim 1 and the claims that depend from claim 1 are allowable.

### Claim Rejections Under 35 U.S.C. § 102

Previously presented claim(s) 1-2, 5-15, and 20-24 is/are rejected under 35 U.S.C. § 102(a)(2) as allegedly being anticipated by Howerton et. al., WO 2019036503 A1, publ. 2/21/2019 (cited in an earlier IDS).

As above, Applicant amends claim 1 to incorporate the subject matter of claim 4, which the Office deemed allowable subject matter if rewritten, as above. As such, Applicant respectfully requests withdrawal of the anticipation rejection.

## CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (858) 350-2240.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 50535-710.304).

Respectfully submitted,

Date: November 24, 2025 By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79,641

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone: (650) 493-9300
Customer No. 21971

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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Mailstop Amendment
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P.O. Box 1450
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## AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

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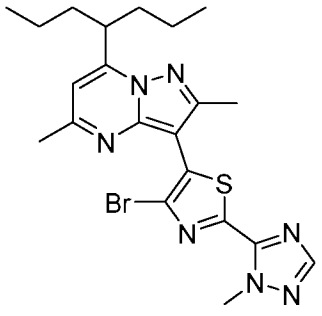
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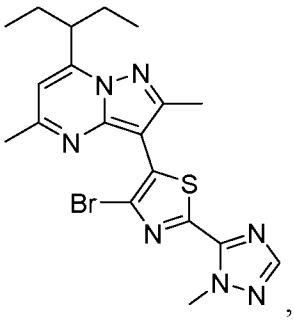
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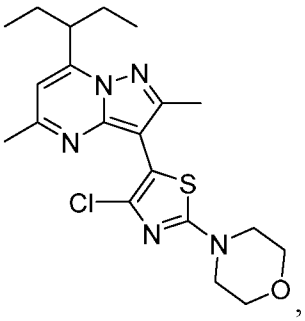
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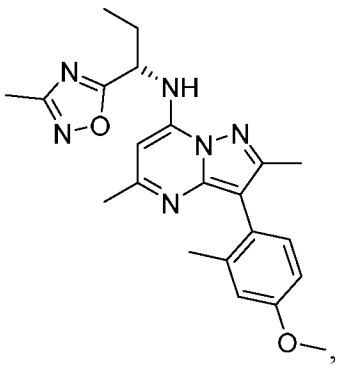
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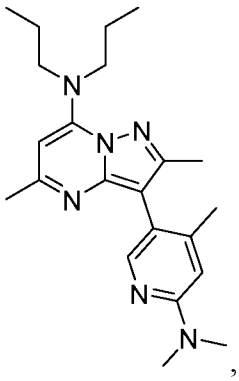
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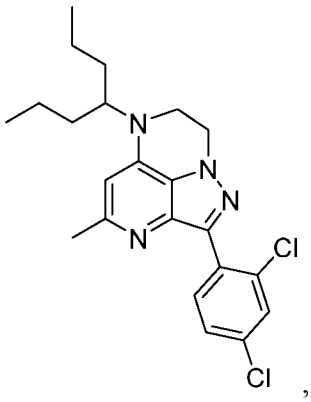
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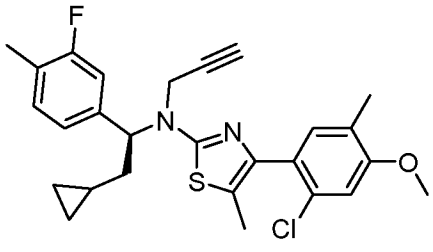
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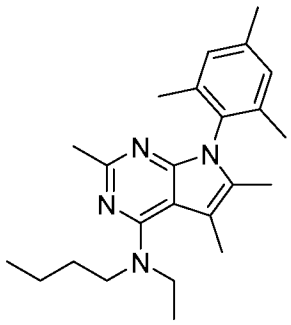
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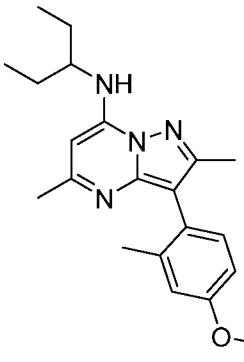
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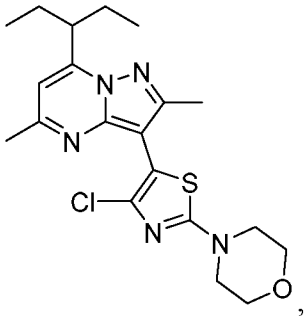

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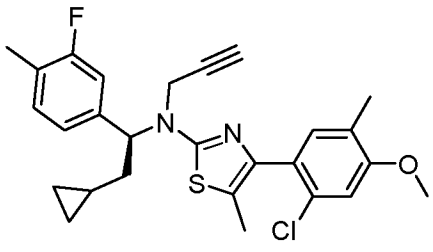

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22. (Previously Presented) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered less than about 6 hours before sleep.
23. (Previously Presented) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered less than about 3 hours before sleep.
24. (Previously Presented) The method of claim 1, wherein the small molecule $CRF_1$ antagonist is administered in the evening.

## REMARKS

Claims 1-15 and 20-24 were pending prior to entry of the amendments presented in this response. Claim 1 has been amended herein to incorporate the subject matter of dependent claim 4. As such, claim 4 is canceled herein. No new matter is believed to be added by way of the amendment made herein. Accordingly, upon entry of the proposed amendments, claims 1-3, 5-15, and 20-24 will be under examination.

### Allowable Subject Matter

Claims 3 and 4 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Without conceding to the basis of any rejections made in the Office Action, and for the purpose of compact prosecution, Applicant amends claim 1 to incorporate the subject matter of dependent claim 4. Accordingly, Applicant respectfully submits amended claim 1 and the claims that depend from claim 1 are allowable.

### Claim Rejections Under 35 U.S.C. § 102

Previously presented claim(s) 1-2, 5-15, and 20-24 is/are rejected under 35 U.S.C. § 102(a)(2) as allegedly being anticipated by Howerton et. al., WO 2019036503 A1, publ. 2/21/2019 (cited in an earlier IDS).

As above, Applicant amends claim 1 to incorporate the subject matter of claim 4, which the Office deemed allowable subject matter if rewritten, as above. As such, Applicant respectfully requests withdrawal of the anticipation rejection.

## CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (858) 350-2240.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 50535-710.304).

Respectfully submitted,

Date: November 24, 2025 By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79,641

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone: (650) 493-9300
Customer No. 21971

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **11/24/2025 04:01:47 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | Colleen Mensching |
| PATENT CENTER # | 73306944 | FILING DATE | 01/31/2025 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Victoria Cheng |

## Documents

**TOTAL DOCUMENTS: 3**

| DOCUMENT | | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|---|
| Spruce 50535-710.304 Non-Final Office Action Response.pdf | | 6 | - | 146 KB |
| Spruce 50535-710.304 Non-Final Office Action Response-A....pdf | (1-1) | 1 | Amendment/Request for Reconsideration-After Non-Final Rejection | 96 KB |
| Spruce 50535-710.304 Non-Final Office Action Response-CLM.pdf | (2-4) | 3 | Claims | 137 KB |
| Spruce 50535-710.304 Non-Final Office Action Response-REM.pdf | (5-6) | 2 | Applicant Arguments/Remarks Made in an Amendment | 98 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| Spruce 50535-710.304 Non-Final Office Action Response.pdf | CF58DB4353B781FFE3CBD3F383AE1C71B3DCB48C1F2539C342E14B6C057DD1BDD29E60E697FD49418B445994F8E9F423B5A42A965A350ADCDAF0B4F102065F97 |
| Spruce 50535-710.304 Non-Final Office Action Response-A....pdf | 51A2AA0540D11A7417AFB1D1B5DD60630915605DC3A18E3567DB733097E3EAFB9FEE84A0B25E8D13A0881E87D7680B4564D146113BD191F8319C36AE49FE3067 |
| Spruce 50535-710.304 Non-Final Office Action Response-CLM.pdf | 7E7905102B78B8CF4522AB5B3466089F2A009B0CBDA144499AA36350EBE13C0CF889D630939A782E9FAAFAF16093F6F49B172BE9BB7B4AE6CB399B16A86F0E5E |
| Spruce 50535-710.304 Non-Final Office Action Response-REM.pdf | 93E4D0BACDCC803F8CA21630826A4BF272C49F4F8BF80BDACC1FA7DEC4EB2BCA55F6F1A2D679ABA0453CAA72CD037B2BA9C39C2F45FEF3A4D6BC1F89E202D65D |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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# NOTICE OF ALLOWANCE AND FEE(S) DUE

21971 7590 12/23/2025

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER | |
|---|---|
| PIHONAK, SARAH | |
| ART UNIT | PAPER NUMBER |
| 1627 | |

DATE MAILED: 12/23/2025

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 19/043,275 | 01/31/2025 | Alexis HOWERTON | 50535-710.304 | 5486 |

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1290 | $0.00 | $0.00 | $1290 | 03/23/2026 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.**

## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 12/23/2025
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650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

| (Typed or printed name) |
|---|
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 19/043,275 | 01/31/2025 | Alexis HOWERTON | 50535-710.304 | 5486 |

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1290 | $0.00 | $0.00 | $1290 | 03/23/2026 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| PIHONAK, SARAH | 1627 | 514-233200 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES DEPARTMENT OF COMMERCE
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 19/043,275 | 01/31/2025 | Alexis HOWERTON | 50535-710.304 | 5486 |

21971 7590 12/23/2025

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER | |
|---|---|
| PIHONAK, SARAH | |
| ART UNIT | PAPER NUMBER |
| 1627 | |

DATE MAILED: 12/23/2025

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/ owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

| Notice of Allowability | Application No. 19/043,275 | Applicant(s) HOWERTON et al. | |
|---|---|---|---|
| | Examiner SARAH PIHONAK | Art Unit 1627 | AIA (First Inventor to File) Status Yes |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 11/24/25.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-3,5-15 and 20-24 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   **Certified copies:**

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

***Notice of Pre-AIA or AIA Status***

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

***Status of Claims***

1. Claims 1-3, 5-15, and 20-24 are pending as of the response and amendments filed on 11/24/25. Claims 4 and 16-19 have been canceled.

The 102(a)(2) rejection of record over Howerton is withdrawn in consideration of the amendments.

The objection to claims 3-4 is withdrawn in view of the amended claims.

2. Claims 1-3, 5-15, and 20-24 are allowed.

***Reasons for Allowance***

3. The following is an examiner's statement of reasons for allowance: the claimed method is not taught or suggested by the prior art. Howerton, WO 2019036503; and Grigoriadis, US 20170020877, both of record, represent the closest prior art. Howerton and Grigoriadis teach treatment of congenital adrenal hyperplasia by administering a CRF1 receptor antagonist, however, treatment of a subject having an ovarian adrenal rest tumor or a testicular adrenal rest tumor, as required by the claims, is not taught or suggested.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the

issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

### *Information Disclosure Statements*

4. The IDS filed on 10/3/25 and 11/24/25 have been considered.

### *Correspondence*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached Monday-Friday 9:00-5:30 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached at 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for

information about filing in DOCX format. For additional questions, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO

Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SARAH . PIHONAK
Primary Examiner
Art Unit 1627

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 19/043,275 | HOWERTON et al. |
| | Examiner | Art Unit |
| | SARAH PIHONAK | 1627 |

| CPC - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| a61k31/519; a61p5/06,08 | 05/28/2025 | s.p. |
| a61k31/519,5377; a61p5/06,08; a61p35/00 | 09/03/2025 | s.p. |
| a61k31/519,5377; a61k9/0053,20,2004,48,4841; a61p5/06,08; a61p35/00 | 12/09/2025 | s.p. |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| | | |

| US Classification - Searched* | | | |
|---|---|---|---|
| **Class** | **Subclass** | **Date** | **Examiner** |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| | |
|---|---|
| /SARAH PIHONAK/<br>Primary Examiner, Art Unit 1627 | |

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 19/043,275 | HOWERTON et al. |
| | Examiner | Art Unit |
| | SARAH PIHONAK | 1627 |

| Search Notes | | |
|---|---|---|
| **Search Notes** | **Date** | **Examiner** |
| a61k31/519; a61p5/06,08 | 05/28/2025 | s.p. |
| inventor & applicant search in PE2E, patent data portal | 05/28/2025 | s.p. |
| invention & claims search in stn, PE2E | 05/28/2025 | s.p. |
| a61k31/519,5377; a61p5/06,08; a61p35/00 | 09/03/2025 | s.p. |
| inventor & applicant search in PE2E, patent data portal | 09/03/2025 | s.p. |
| invention & claims search in stnext, PE2E (incl. similarity search | 09/03/2025 | s.p. |
| a61k31/519,5377; a61k9/0053,20,2004,48,4841; a61p5/06,08; a61p35/00 | 12/09/2025 | s.p. |
| inventor & applicant search in PE2E, patent data portal | 12/09/2025 | s.p. |
| invention & claims search in PE2E (incl. similarity search) | 12/09/2025 | s.p. |
| STIC search results | 09/10/2025 | s.p. |

| Interference Search | | | |
|---|---|---|---|
| **US Class/CPC Symbol** | **US Subclass/CPC Group** | **Date** | **Examiner** |
| a61k | 31/519,5377; 9/0053,20,2004,48,4841 | 12/09/2025 | s.p. |
| a61p | 5/06,08; 35/00 | 12/09/2025 | s.p. |

| | |
|---|---|
| /SARAH PIHONAK/<br>Primary Examiner, Art Unit 1627 | |

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 19/043,275 | HOWERTON et al. |
| | **Examiner** | **Art Unit** |
| | SARAH PIHONAK | 1627 |

| CPC | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Symbol** | | | | | | | **Type** | **Version** |
| A61K | / | 31 | / | 519 | | | F | 2013-01-01 |
| A61K | / | 9 | / | 0053 | | | A | 2013-01-01 |
| A61K | / | 9 | / | 20 | | | A | 2013-01-01 |
| A61K | / | 9 | / | 48 | | | A | 2013-01-01 |
| A61K | / | 45 | / | 06 | | | A | 2013-01-01 |
| A61P | / | 5 | / | 06 | | | A | 2018-01-01 |
| A61P | / | 5 | / | 08 | | | A | 2018-01-01 |

| CPC Combination Sets | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Symbol** | | | | | **Type** | **Set** | **Ranking** | **Version** |
| | / | | / | | | | | |

| NONE | | Total Claims Allowed: | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 19 | |
| /SARAH PIHONAK/<br>Primary Examiner, Art Unit 1627 | 09 December 2025 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | None |

U.S. Patent and Trademark Office — Part of Paper No.: 20251209

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 19/043,275 | HOWERTON et al. |
| | Examiner | Art Unit |
| | SARAH PIHONAK | 1627 |

| INTERNATIONAL CLASSIFICATION | | | | |
|---|---|---|---|---|
| CLAIMED | | | | |
| A61K | / | 31 | / | 519 |
| A61K | / | 9 | / | 00 |
| A61K | / | 9 | / | 20 |
| A61K | / | 9 | / | 48 |
| A61P | / | 5 | / | 06 |
| A61P | / | 5 | / | 08 |

| NON-CLAIMED | | | | |
|---|---|---|---|---|
| | / | | / | |

| US ORIGINAL CLASSIFICATION | |
|---|---|
| CLASS | SUBCLASS |
| | |

| CROSS REFERENCES(S) | | | | | | |
|---|---|---|---|---|---|---|
| CLASS | SUBCLASS (ONE SUBCLASS PER BLOCK) | | | | | |
| | | | | | | |

| NONE | | Total Claims Allowed: | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 19 | |
| /SARAH PIHONAK/<br>Primary Examiner, Art Unit 1627 | 09 December 2025 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | None |

U.S. Patent and Trademark Office

Part of Paper No.: 20251209

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 19/043,275 | HOWERTON et al. |
| | Examiner | Art Unit |
| | SARAH PIHONAK | 1627 |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 9 | 10 | | 19 | | | | | | | | | | |
| 2 | 2 | 10 | 11 | 15 | 20 | | | | | | | | | | |
| 3 | 3 | 11 | 12 | 16 | 21 | | | | | | | | | | |
| | 4 | 12 | 13 | 17 | 22 | | | | | | | | | | |
| 4 | 5 | 13 | 14 | 18 | 23 | | | | | | | | | | |
| 5 | 6 | 14 | 15 | 19 | 24 | | | | | | | | | | |
| 6 | 7 | | 16 | | | | | | | | | | | | |
| 7 | 8 | | 17 | | | | | | | | | | | | |
| 8 | 9 | | 18 | | | | | | | | | | | | |

| | | | |
|---|---|---|---|
| NONE | | **Total Claims Allowed:** | |
| (Assistant Examiner) | (Date) | 19 | |
| /SARAH PIHONAK/<br>Primary Examiner, Art Unit 1627 | 09 December 2025 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | None |

U.S. Patent and Trademark Office

Part of Paper No.: 20251209

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 1 | of | 5 | Attorney Docket Number | 50535-710.304 |

**U. S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | None | | | |

**FOREIGN PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

| EXAMINER SIGNATURE | | | |
|---|---|---|---|
| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 12/09/2025 |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 2 | of | 5 | Attorney Docket Number | 50535-710.304 |

| NON-PATENT LITERATURE DOCUMENTS | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 001 | BRADLEY, D. Anawalt et al. Chapter 12: Testes. Greenspan's Basic & Clinical Endocrinology. 10th ed. New York: McGraw-Hill Education (pp. 413-442) (2018). | ☐ |
| | 002 | EP3784233 Case Details for ACT_34386/2025 (1 pg) (2025). | ☐ |
| | 003 | FDA Approves New Treatment for Congenital Adrenal Hyperplasia, US Food and Drug Administration, December 13, 2024. Available at URL: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-congenital-adrenal-hyperplasia? pp.1-2. | ☐ |
| | 004 | SPEISER, Phyllis W. et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism 103(11):4043-4088 (2018). | ☐ |
| | 005 | Spruce Power Holding Corporation. Quarterly Report (Form 10-Q) for the period ended June 30, 2024. United States Securities and Exchange Commission, August 13, 2024. Available at: https://www.sec.gov/Archives/edgar/data/1772720/000162828024037238/spru-20240630.htm pp. 1-53. | ☐ |
| | 006 | U.S. Serial No. 19/043,264 Office Action dated August 18, 2025. | ☐ |
| | 007 | U.S. Serial No. 19/043,303 Office Action dated September 5, 2025. | ☐ |
| | 008 | World Health Organization. Drug Information 33(1):122 (2019). | ☐ |

| EXAMINER SIGNATURE | | | |
|---|---|---|---|
| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 12/19/2025 |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 3 | of | 5 | Attorney Docket Number | 50535-710.304 |

**TIMING STATEMENT**

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

**TIMING FEE**

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

**COPIES**

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

**SIZE FEE ASSERTION**

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

| Signature: | /Kaia R. Parenti/ | Date (YYYY-MM-DD) | 2025-10-03 |
|---|---|---|---|
| Name/Print | Kaia R. Parenti | Registration Number | 81050 |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 4 | of | 5 | Attorney Docket Number | 50535-710.304 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

# PE2E SEARCH - Search History (Prior Art)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| L1 | 19 | ("10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220143037" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn. | (US-PGPUB; USPAT) | OR | ON | ON | 2025/05/16 04:02 PM |
| L2 | 390 | (a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND ((administer* OR administration* OR provid* OR deliver* OR treat*) WITH (fed OR fasted OR fasting OR food*)) | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/05/28 08:58 AM |
| L3 | 473 | (a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND ((endocrine OR hormone OR hormonal) WITH (disease* OR disorder* OR condition* OR syndrome*)) | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/05/28 09:10 AM |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| L4 | 31 | ((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM. | (US-PGPUB; USPAT) | OR | ON | ON | 2025/05/28 09:26 AM |
| L5 | 21 | ((("HOWERTON") near3 ("Alexis"))).INV. | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/05/28 09:26 AM |
| L6 | 21 | ((("GERBER") near3 ("Hal"))).INV. | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/05/28 09:27 AM |
| L7 | 8 | (a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND ((endocrine OR hormone OR hormonal) WITH (disease* OR disorder* OR condition* OR syndrome*)) AND (L4 OR L5 OR L6) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/05/28 09:27 AM |
| L8 | 8 | (a61k31/519 OR a61p5/06,08).cpc. AND (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND (congenital adj4 adrenal adj4 hyperplasia) AND (L4 OR L5 OR L6) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/05/28 09:31 AM |
| L9 | 28 | (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND (congenital adj4 adrenal adj4 hyperplasia) AND (L4 OR L5 OR L6) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/05/28 09:31 AM |
| L10 | 4721 | (corticotropin adj8 releasing adj8 factor adj8 antagon*) AND ((administer* OR administration* OR provid* OR deliver* OR treat*) WITH (fed OR fasted OR fasting OR food*)) | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/05/28 09:32 AM |
| L11 | 406 | (corticotropin adj8 releasing adj8 factor adj8 antagon*).ab,ti,clm. AND L10 | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, | OR | ON | ON | 2025/05/28 09:32 AM |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | | | | |
| L12 | 54 | ("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR "20210361664" OR "20220133742" OR "20220143037" OR "20230159533" OR "20230321112" OR "20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177403" OR "20250195527" OR "8030304" OR "8563718" OR "10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220211711" OR "4328245" OR | (US-PGPUB; USPAT) | OR | ON | ON | 2025/08/28 02:19 PM |

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|---|---|---|---|---|---|---|---|
| | | "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn. | | | | | |
| L13 | 38 | L12 AND (food OR fed OR eat OR eaten OR meal OR ingest$3) | (US-PGPUB; USPAT) | OR | ON | ON | 2025/08/28 02:24 PM |
| L14 | 1 | "20250177404".pn. | (US-PGPUB) | OR | ON | ON | 2025/09/03 10:37 AM |
| L15 | 30 | (Artificial Intelligence) More like doc: US-20250177404-A1<br>Text: (JP-H0971528-A OR WO-2007109853-A1 OR BR-PI0717023-B8 OR US-20100203048-A1 OR CN-106102740-A OR TW-202400179-A OR EA-202090450-A1 OR US-20250177403-A1 OR US-20250195527-A1 OR EP-3784233-B1 OR HK-40040045-A OR US-20250177404-A1 OR HK-40040045-B OR AU-2023203095-A1 OR US-20240285593-A1 OR US-11304952-B2 OR US-11304950-B2 OR CA-3098562-A1 OR US-20220211711-A1 OR WO-2017087610-A1).did. | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/09/03 10:37 AM |
| L16 | 10 | L15 AND (corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR suppress* OR decreas* OR reduc*)) AND ((administer* OR administrat* OR provid* OR given OR giving OR gave OR deliver*) adj15 (food OR eat OR fed OR fast$3)) | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/09/03 10:39 AM |
| L17 | 3923 | (a61k31/519,5377 OR a61p5/06,08 OR a61p35/00).cpc. AND | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, | OR | ON | ON | 2025/09/03 10:41 AM |

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|---|---|---|---|---|---|---|---|
| | | (corticotropin adj12 releas* adj12 factor adj12 (antagon* OR inhibit* OR decreas* OR reduc*)) | CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | | | | |
| L18 | 774 | L17 AND ((administer* OR administrat* OR provid* OR given OR giving OR gave OR deliver*) adj15 (food OR eat OR fed OR fast$3)) | (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/09/03 10:42 AM |
| L19 | 220 | ((@pd OR @ptad OR @prad OR @ad OR @rlad)< ("20180427")) AND L18 | (US-PGPUB; USPAT) | OR | ON | ON | 2025/09/03 11:08 AM |
| L20 | 54 | ("11708372" OR "11858932" OR "12098152" OR "20020013357" OR "20030008885" OR "20050209250" OR "20060078623" OR "20090076266" OR "20100022560" OR "20100155595" OR "20110136865" OR "20110160168" OR "20110166345" OR "20130045979" OR "20170333126" OR "20180110554" OR "20190262349" OR "20200255436" OR "20210015827" OR "20210038604" OR "20210137935" OR "20210322430" OR "20210361664" OR "20220133742" OR | (US-PGPUB; USPAT) | OR | ON | ON | 2025/09/03 11:34 AM |

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|---|---|---|---|---|---|---|---|
| | | "20220143037" OR "20230159533" OR "20230321112" OR "20230414627" OR "20240043432" OR "20240261300" OR "20240293421" OR "20250064812" OR "20250177403" OR "20250195527" OR "8030304" OR "8563718" OR "10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn. | | | | | |
| L21 | 33 | L20 AND ((administer* OR administrat* OR provid* OR given OR giving OR gave OR deliver*) adj15 (food OR eat OR fed OR fast$3)) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/09/03 11:37 AM |
| L22 | 35 | ((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM. | (US-PGPUB; USPAT) | OR | ON | ON | 2025/09/03 11:57 AM |
| L23 | 24 | ((("HOWERTON") near3 ("Alexis")) OR (("GERBER") near3 ("Hal"))).INV. | (US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT) | OR | ON | ON | 2025/09/03 11:57 AM |
| L24 | 32 | (L22 OR L23) AND (corticotropin adj12 releas* adj12 factor adj12 (antagon* OR inhibit* OR decreas* OR reduc*)) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/09/03 11:58 AM |
| L25 | 32 | L24 AND ((administer* OR administrat* OR provid* OR given OR giving OR gave OR deliver*) adj15 (food OR eat OR fed OR fast$3)) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/09/03 11:58 AM |
| L26 | 6 | ("11304950" OR | (USPAT) | OR | ON | ON | 2025/09/09 |

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|---|---|---|---|---|---|---|---|
| | | "11858932" OR "12098152" OR "11311549" OR "11344557" OR "11351177").pn. | | | | | 04:32 PM |
| L27 | 1 | "6586456".pn. | (USPAT) | OR | ON | ON | 2025/12/09 02:23 PM |
| L28 | 1 | "20250177404".pn. | (US-PGPUB) | OR | ON | ON | 2025/12/09 03:06 PM |
| L29 | 28 | (Artificial Intelligence) More like doc: US-20250177404-A1 Text: (JP-H0971528-A OR EP-2004205-A4 OR EP-2094709-B1 OR US-20100203048-A1 OR JP-7285222-B2 OR AU-2018317398-A1 OR HK-40040045-B OR US-20250195527-A1 OR US-20250177403-A1 OR US-20250177404-A1 OR EP-3784233-B1 OR HK-40040045-A OR CA-3098562-A1 OR US-20240285593-A1 OR US-11304950-B2 OR US-20210038604-A1 OR AU-2023203095-A1 OR US-11304952-B2 OR JP-7427655-B2 OR US-20220211711-A1).did. | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/12/09 03:06 PM |
| L30 | 10 | L29 AND (corticotropin adj6 releas* adj6 factor adj6 (antagon* OR inhibit* OR block* OR suppress* OR reduc* OR decreas*)) AND (adrenal adj6 rest adj6 (tumor* OR neoplasm* OR growth*)) | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | OR | ON | ON | 2025/12/09 03:08 PM |
| L31 | 37 | (a61k31/519,5377 OR a61k9/0053,20,2004,48,4841 OR a61p5/06,08 OR a61p35/00).cpc. AND (adrenal adj8 rest | (US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, | OR | ON | ON | 2025/12/09 03:12 PM |

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|---|---|---|---|---|---|---|---|
| | | adj8 (tumor* OR neoplasm* OR proliferat* OR growth*)) AND (corticotropin adj8 releas* adj8 factor adj8 (antagon* OR block* OR suppress* OR reduc* OR decreas* OR inhibit*)) | EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB) | | | | |
| L32 | 35 | ((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM. | (US-PGPUB; USPAT) | OR | ON | ON | 2025/12/09 03:14 PM |
| L33 | 24 | ((("HOWERTON") near3 ("Alexis"))).INV. | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/12/09 03:14 PM |
| L34 | 24 | ((("GERBER") near3 ("Hal"))).INV. | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/12/09 03:15 PM |
| L35 | 8 | (L32 OR L33 OR L34) AND (adrenal adj8 rest adj8 (tumor* OR neoplasm* OR proliferat* OR growth*)) AND (corticotropin adj8 releas* adj8 factor adj8 (antagon* OR block* OR suppress* OR reduc* OR decreas* OR inhibit*)) | (US-PGPUB; USPAT; USOCR) | OR | ON | ON | 2025/12/09 03:15 PM |

## PE2E SEARCH - Search History (Interference)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | British Equivalents | Time Stamp |
|---|---|---|---|---|---|---|---|
| N1 | 1038 | (a61k31/519,5377 OR a61p5/06,08 OR a61p35/00).cpc. AND (corticotropin adj12 releas* adj12 factor adj12 (antagon* OR inhibit* OR decreas* OR reduc*)) | (US-PGPUB; USPAT) | OR | ON | ON | 2025/09/03 11:55 AM |
| N2 | 245 | N1 AND ((administer* OR administrat* OR provid* OR given OR giving OR gave OR deliver*) adj15 (food OR eat OR fed OR fast$3)) | (US-PGPUB; USPAT) | OR | ON | ON | 2025/09/03 11:55 AM |
| N3 | 16 | (adrenal adj8 rest adj8 (tumor* OR neoplasm* OR proliferat* OR growth*)) AND (corticotropin adj8 releas* adj8 factor adj8 (antagon* OR block* | (US-PGPUB; USPAT) | OR | ON | ON | 2025/12/09 03:13 PM |

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|---|---|---|---|---|---|---|---|
| | | OR suppress* OR reduc* OR decreas* OR inhibit*)) | | | | | |

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 1 | of | 8 | Attorney Docket Number | 50535-710.304 |

| U. S. PATENT DOCUMENTS | | | | | |
|---|---|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
| | 001 | US-6586456 | 07-01-2003 | FONTAINE; Evelyne et al. | |

| FOREIGN PATENT DOCUMENTS | | | | | | |
|---|---|---|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
| | | None | | | | |

| EXAMINER SIGNATURE | | | |
|---|---|---|---|
| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 12/09/2025 |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 2 | of | 8 | Attorney Docket Number | 50535-710.304 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 001 | ÇAKIR et al., Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia. J Clin Res Pediatr Endocrinol 4(2):94-100 (2012). | ☐ |
| | 002 | ANAWALT, Bradley D. et al. Chapter 12: Testes. Extract from Textbook: Gardner & Shoback, Greenspan's Basic & Clinical Endocrinology, 10th ed. (McGraw-Hill Education), pps. 413, 440-441 (2018). | ☐ |
| | 003 | BACON et al., Effect of Cortisol Treatment on Hormonal Relationships in Congenital Adrenal Hyperplasia. Clinical Endocrinology 6:113-126 (1977). | ☐ |
| | 004 | BENVENGA et al., Testicular adrenal rests: evidence for luteinizing hormone receptors and for distinct types of testicular nodules differing for their autonomization. European Journal of Endocrinology 141:231-237 (1999). | ☐ |
| | 005 | BHATT, Deepak L. et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. N Engl J Med 370(15):1393-401 (2014). | ☐ |
| | 006 | BROWN, Marie T. et al. Medication Adherence: WHO Cares? Mayo Clin Proc 86(4):304-314 (2011). | ☐ |
| | 007 | Chemical Abstracts Service. CAS Registry: 752253-39-7. 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-((1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-2-propyn-1-yl-2-thiazolamine: pp. 1-35. STN Entry Date October 11, 2005. Retrieved October 14, 2025. Retrieved from :https://pubchem.ncbi.nlm.nih.gov/compound/5282340. | ☐ |
| | 008 | CLAAHSEN et al., Testicular Tumors in Patients with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency Show Functional Features of Adrenocortical Tissue. J Clin Endocrinol Metab. 92(9):3674-80 (2007). | ☐ |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 12/19/2025 |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 3 | of | 8 | Attorney Docket Number | 50535-710.304 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 009 | Clinical Study Protocol SPR001-201. A Phase 2, Multiple-Dose, Dose-Escalation Study to Evaluate the Safety and Efficacy of SPR001 in Adults with Classic Congenital Adrenal Hyperplasia (CAH). (8/23/2018). | ☐ |
| | 010 | Declaration of Associate Professor Dr Henrik Falhammar dated November 14, 2025. | ☐ |
| | 011 | Declaration of Professor Peter Hindmarsh dated October 23, 2025. | ☐ |
| | 012 | Declaration of Vivian H. Lin, M.D. dated November 14, 2025. | ☐ |
| | 013 | FEDOROVA, Olga et al. What is the need for adrenalectomy in patients with congenital adrenal hyperplasia in the era of CRF1/ACT inhibitors? Frontiers in Endocrinology (Lausanne) 16:1693063, 1-10 (2025). | ☐ |
| | 014 | GUPTA et al., Corticosteroid Physiology and Principles of Therapy. Indian J Pediatr 75(10):1039-1044 (2008). | ☐ |
| | 015 | GWATHMEY et al., Glucocorticoid-Induced Fetal Programming Alters the Functional Complement of Angiotensin Receptor Subtypes Within the Kidney. Hypertension 57(3):620-6 (2011). | ☐ |
| | 016 | Henrik Falhammar, M.D., Ph.D., FRACP, Curriculum Vitae (No date available). | ☐ |
| | 017 | HINDMARSH et al., Congenital Adrenal Hyperplasia A Comprehensive Guide. Elsevier, ISBN: 978-0-12-811483-4 (pp. 263-264 and 319-320) (2017). | ☐ |
| | 018 | MATSUBARA. Pathophysiological Role of Angiotensin II Type 2 Receptor in Cardiovascular and Renal Diseases. Circ Res. 83:1182-1191 (1998). | ☐ |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 12/19/2025 |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 4 | of | 8 | Attorney Docket Number | 50535-710.304 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 019 | MEENA, H. et al., Growth Pattern and Clinical Profile of Indian Children with Classical 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia on Treatment. Indian J Pediatr. 86(6):496-502 (2019). | ☐ |
| | 020 | MESA et al., Immunophenotypic differences between neoplastic and non-neoplastic androgen-producing cells containing and lacking Reinke crystals. Virchows Arch. 469(6):679-686 (2016). | ☐ |
| | 021 | MORRIS, David. Steroid-induced Diabetes and Hyperglycaemia. Part 1: Mechanisms and Risks. Diabetes & Primary Care 20(4):151-153 (2018). | ☐ |
| | 022 | NAGURNEY et al., The Accuracy and completeness of Data Collected by Prospective and Retrospective Methods. ACAD EMERG MED 12(9):884-95 (September 2005). | ☐ |
| | 023 | Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Denying Institution of Inter Partes Review in U.S. Patent No. 12,115,166 dated October 03, 2025 (pp 1-3) (PGR-2025-00032). | ☐ |
| | 024 | NEWFIELD, Ron S. et al. Crinecerfont, a CRF1 Receptor Antagonist, Lowers Adrenal Androgens in Adolescents with Congenital Adrenal Hyperplasia. The Journal of Clinical Endocrinology & Metabolism 108(11):2871-2878 (2023). | ☐ |
| | 025 | POYRAZOGLU et al., Prevalence of testicular microlithiasis in males with congenital adrenal hyperplasia and its association with testicular adrenal rest tumors. Horm Res Paediatr. 73:443-448 (2010). | ☐ |
| | 026 | Regulation (EC) No 141/2000 Of the European Parliament and of the Council of 16 December 1999 on orphan medical products (pp. 1-5). | ☐ |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 12/19/2025 |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 5 | of | 8 | Attorney Docket Number | 50535-710.304 |

**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
|---|---|---|---|
| | 027 | SOWERS et al., Effect of dexamethasone on gonadotropin responsiveness to luteinizing hormone-releasing hormone and clomiphene in women with secondary amenorrhea. Am J Obstet Gynecol. 134(3):325-8 (1979 Jun 1). | ☐ |
| | 028 | SPIERLING, Samantha R, and Eric P Zorrilla. et al. Don't stress about CRF: Assessing the translational failures of CRF1 antagonists. Psychopharmacology 234(9-10):1467-1481 (2017). | ☐ |
| | 029 | U.S. Serial No. 17/578,149 Office Action dated October 6, 2025. | ☐ |
| | 030 | U.S. Serial No. 18/438,060 Office Action dated October 7, 2025. | ☐ |
| | 031 | Vivian H. Lin, Curriculum Vitae (No date available). | ☐ |
| | 032 | XAVIER et al., Gene Expression Control by Glucocorticoid Receptors during Innate Immune Responses. Front. Endocrinol. 7:31 (2016). | ☐ |
| | 033 | XUE et al. Glucocorticoid Modulates Angiotensin II Receptor Expression Patterns and Protects the Heart from Ischemia and Reperfusion Injury. PLoS One 9(9):e106827 (2014). | ☐ |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 12/19/2025 |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 6 | of | 8 | Attorney Docket Number | 50535-710.304 |

## TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

## TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

## COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

## SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

| Signature: | /Victoria Cheng/ | Date (YYYY-MM-DD) | 2025-11-24 |
|---|---|---|---|
| Name/Print | Victoria Cheng | Registration Number | 79641 |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
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| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 7 | of | 8 | Attorney Docket Number | 50535-710.304 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | HOWERTON; Alexis et al. | Group Art Unit: | 1627 |
| Serial Number: | 19/043,275 | Examiner: | PIHONAK, SARAH |
| Filing or 371 (c) Date: | 2025-01-31 | **CONFIRMATION NO:** | **5486** |
| Title: | METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS | | |

**FILED ELECTRONICALLY ON: January 12, 2026**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☒ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☒ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☒ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: January 12, 2026

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

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|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 1 | of | 5 | Attorney Docket Number | 50535-710.304 |

**U. S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | None | | | |

**FOREIGN PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

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| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 2 | of | 5 | Attorney Docket Number | 50535-710.304 |

| **NON-PATENT LITERATURE DOCUMENTS** | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 001 | DEAK, T. et al. The impact of the nonpeptide corticotropin-releasing hormone antagonist antalarmin on behavioral and endocrine responses to stress. Endocrinology 140(1):79-86 (1999). | ☐ |
| | 002 | U.S. Serial No. 18/078,649 Office Action dated November 18, 2025. | ☐ |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

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| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 3 | of | 5 | Attorney Docket Number | 50535-710.304 |

**TIMING STATEMENT**

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1). **NPL Ref. 001**

**OR**

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2). **NPL Ref. 002**

☐ See attached timing statement under 37 CFR 1.97(e).

☐ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

**TIMING FEE**

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

**COPIES**

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

**SIZE FEE ASSERTION**

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☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

| Signature: | /Victoria Cheng/ | Date (YYYY-MM-DD) | 2025-01-12 |
|---|---|---|---|
| Name/Print | Victoria Cheng | Registration Number | 79641 |

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 4 | of | 5 | Attorney Docket Number | 50535-710.304 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Inventor: | HOWERTON; Alexis et al. | Group Art Unit: | 1627 |
| Serial Number: | 19/043,275 | Examiner: | PIHONAK, SARAH |
| Filing or 371 (c) Date: | 2025-01-31 | **CONFIRMATION NO:** | **5486** |
| Title: | METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS | | |

**FILED ELECTRONICALLY ON: January 12, 2026**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

## INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☒ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☒ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☒ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.304).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: January 12, 2026

By: /Victoria Cheng/
Victoria Cheng, Reg. No. 79641

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 1 | of | 5 | Attorney Docket Number | 50535-710.304 |

**U. S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | None | | | |

**FOREIGN PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

| EXAMINER SIGNATURE | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
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| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 2 | of | 5 | Attorney Docket Number | 50535-710.304 |

| **NON-PATENT LITERATURE DOCUMENTS** | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 001 | DEAK, T. et al. The impact of the nonpeptide corticotropin-releasing hormone antagonist antalarmin on behavioral and endocrine responses to stress. Endocrinology 140(1):79-86 (1999). | ☐ |
| | 002 | U.S. Serial No. 18/078,649 Office Action dated November 18, 2025. | ☐ |

| **EXAMINER SIGNATURE** | | | |
|---|---|---|---|
| Examiner Signature | | Date Considered | |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PTO/SB/08 (01-25)
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| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 3 | of | 5 | Attorney Docket Number | 50535-710.304 |

## TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1). **NPL Ref. 001**

**OR**

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2). **NPL Ref. 002**

☐ See attached timing statement under 37 CFR 1.97(e).

☐ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

## TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

## COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

## SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

| Signature: | /Victoria Cheng/ | Date (YYYY-MM-DD) | 2025-01-12 |
|---|---|---|---|
| Name/Print | Victoria Cheng | Registration Number | 79641 |

PTO/SB/08 (01-25)
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| Sheet | 4 | of | 5 | Attorney Docket Number | 50535-710.304 |

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **01/12/2026 04:47:31 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | JENNIFER VAIL |
| PATENT CENTER # | 73941936 | AUTHORIZED BY | Victoria Cheng |
| CUSTOMER # | 21971 | FILING DATE | 01/31/2025 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | Alexis HOWERTON |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| **DA / 232415** | **E20261BG47548842** | **JENNIFER VAIL** |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1806 | SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT | 280.00 | 1 | 280.00 |
| | | | **TOTAL AMOUNT:** | **$280.00** |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **01/12/2026 04:47:31 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

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| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Victoria Cheng |

## Documents

**TOTAL DOCUMENTS: 4**

| DOCUMENT | | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|---|
| Spruce 50535-710_304_IDS.pdf | | 9 | - | 271 KB |
| Spruce 50535-710_304_IDS-TRAN.LET.pdf | (1-4) | 4 | Transmittal Letter | 139 KB |
| Spruce 50535-710_304_IDS-IDS.pdf | (5-9) | 5 | Information Disclosure Statement (IDS) Form (SB08) | 128 KB |
| NPL_001_DEAK_Theimpact ofthenonpeptide_79-86.pdf | | 8 | Non Patent Literature | 237 KB |
| NPL_002_US18078649_OA_ 2025_11_18.pdf | | 9 | Non Patent Literature | 329 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| Spruce 50535-710_304_IDS.pdf | CFCC5D9883721C38D1A649CAA83DAD66DF0A0778BBED899E322BC8F1754A0E4779CCC2204B94EE5FDA2D3E861C7111140DD364E6A9A931FCA1D72448BF85DFD5 |
| Spruce 50535-710_304_IDS-TRAN.LET.pdf | C1F9349B3EBB9ACD0DB7F83D0E57722861E80FC90A360535A6BCF1212A5AA8E0C7EABCAB571A1C6852C9B3883031BD5655D3A46E58C72B1D5CE360811C55927A |
| Spruce 50535-710_304_IDS-IDS.pdf | EFF7BF2B414D843CD1636E4448A71FCF90E56058549D51A886C2B0951A4D43ABD9D7724A488A16FB50ADA745A75BFFEB538785FE2F6A2421AC97D36E8B4EB03E |
| NPL_001_DEAK_Theimpactofthenonpeptide_79-86.pdf | 2026260EC20A6B59E3FF10CD7EBD435088D3C600E0F8CAAC995FA37C2DB2866600D995E2F600C1F9772678C8203D020BC9785ADAC0DAEE8AC3365029EFFC1AC2 |
| NPL_002_US18078649_OA_2025_11_18.pdf | 639286B5B1D301D897DE5548AA546802116E2182784620D9883B2CCE48B65840916F5CD30F28A731F80E494D749AD6C22715639CD16D54515CA7ECE5A67C5CED |

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 19/043,275 | 01/31/2025 | Alexis HOWERTON | 50535-710.304 | 5486 |

21971 7590 01/21/2026

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

| EXAMINER | |
|---|---|
| PIHONAK, SARAH | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1627 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 01/21/2026 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

| ***CORRECTED*** ***Notice of Allowability*** | **Application No.** 19/043,275 | **Applicant(s)** HOWERTON et al. | |
|---|---|---|---|
| | **Examiner** SARAH PIHONAK | **Art Unit** 1627 | **AIA (First Inventor to File) Status** Yes |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 1/12/26.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-3,5-15 and 20-24 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   **Certified copies:**

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 1 | of | 5 | Attorney Docket Number | 50535-710.304 |

**U. S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|
| | | None | | | |

**FOREIGN PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | None | | | | |

| EXAMINER SIGNATURE | | | |
|---|---|---|---|
| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 01/15/2026 |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 2 | of | 5 | Attorney Docket Number | 50535-710.304 |

| NON-PATENT LITERATURE DOCUMENTS | | | |
|---|---|---|---|
| Examiner Initials* | Cite No.[1] | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
| | 001 | DEAK, T. et al. The impact of the nonpeptide corticotropin-releasing hormone antagonist antalarmin on behavioral and endocrine responses to stress. Endocrinology 140(1):79-86 (1999). | ☐ |
| | 002 | U.S. Serial No. 18/078,649 Office Action dated November 18, 2025. | ☐ |

| EXAMINER SIGNATURE | | | |
|---|---|---|---|
| Examiner Signature | /SARAH PIHONAK/ | Date Considered | 01/15/2026 |

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 3 | of | 5 | Attorney Docket Number | 50535-710.304 |

## TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1). **NPL Ref. 001**

**OR**

☒ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2). **NPL Ref. 002**

☐ See attached timing statement under 37 CFR 1.97(e).

☐ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

## TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

## COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

## SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

## SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

| Signature: | /Victoria Cheng/ | Date (YYYY-MM-DD) | 2025-01-12 |
|---|---|---|---|
| Name/Print | Victoria Cheng | Registration Number | 79641 |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>(Use as many sheets as necessary) | | | | Complete if Known | |
|---|---|---|---|---|---|
| | | | | Application Number | 19/043,275 |
| | | | | Filing Date | 01-31-2025 |
| | | | | First Named Inventor | HOWERTON; Alexis |
| | | | | Art Unit | 1627 |
| | | | | Examiner Name | PIHONAK, SARAH |
| Sheet | 4 | of | 5 | Attorney Docket Number | 50535-710.304 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P/

## PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21971 7590 12/23/2025

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

| | |
|---|---|
| Jennifer Vail | (Typed or printed name) |
| /jvail/ | (Signature) |
| 2/2/2026 | (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 19/043,275 | 01/31/2025 | Alexis HOWERTON | 50535-710.304 | 5486 |

TITLE OF INVENTION: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | UNDISCOUNTED | $1290 | $0.00 | $0.00 | $1290 | 03/23/2026 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| PIHONAK, SARAH | 1627 | 514-233200 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 WILSON SONSINI GOODRICH & ROSATI
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: SPRUCE BIOSCIENCES, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): South San Francisco, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☑ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☑ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 23-2415

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Kaia R. Parenti/ Date February 2, 2026

Typed or printed name Kaia R. Parenti Registration No. 81050

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

# ELECTRONIC ACKNOWLEDGEMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **02/02/2026 12:12:12 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | JENNIFER VAIL |
| PATENT CENTER # | 74284202 | FILING DATE | 01/31/2025 |
| CUSTOMER # | 21971 | FIRST NAMED INVENTOR | Alexis HOWERTON |
| CORRESPONDENCE ADDRESS | - | AUTHORIZED BY | Kaia Parenti |

## Documents

**TOTAL DOCUMENTS: 1**

| DOCUMENT | PAGES | DESCRIPTION | SIZE (KB) |
|---|---|---|---|
| Spruce 50535-710.304 Issue Fee Transmital.pdf | 1 | Issue Fee Payment (PTO-85B) | 105 KB |

## Digest

| DOCUMENT | MESSAGE DIGEST(SHA-512) |
|---|---|
| Spruce 50535-710.304 Issue Fee Transmital.pdf | 909C2849BD6D7512780F26D32B83BC6FECF8FE9C2C1DB8E83B7AC269B474286C969F5E7BB9082548D029A1F420C858585B8510C1F4F68F4613F9D215C692BAD4 |

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# ELECTRONIC PAYMENT RECEIPT

| APPLICATION # | RECEIPT DATE / TIME | ATTORNEY DOCKET # |
|---|---|---|
| **19/043,275** | **02/02/2026 12:12:12 PM Z ET** | **50535-710.304** |

## Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## Application Information

| | | | |
|---|---|---|---|
| APPLICATION TYPE | Utility - Nonprovisional Application under 35 USC 111(a) | PATENT # | - |
| CONFIRMATION # | 5486 | FILED BY | JENNIFER VAIL |
| PATENT CENTER # | 74284202 | AUTHORIZED BY | Kaia Parenti |
| CUSTOMER # | 21971 | FILING DATE | 01/31/2025 |
| CORRESPONDENCE ADDRESS | - | FIRST NAMED INVENTOR | Alexis HOWERTON |

## Payment Information

| PAYMENT METHOD | PAYMENT TRANSACTION ID | PAYMENT AUTHORIZED BY |
|---|---|---|
| **DA / 232415** | **E202622C12338721** | **JENNIFER VAIL** |

| FEE CODE | DESCRIPTION | ITEM PRICE($) | QUANTITY | ITEM TOTAL($) |
|---|---|---|---|---|
| 1501 | UTILITY ISSUE FEE | 1290.00 | 1 | 1290.00 |
| | | | **TOTAL AMOUNT:** | **$1,290.00** |

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**New Applications Under 35 U.S.C. 111**

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| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 19/043,275 | 03/10/2026 | 12569491 | 50535-710.304 | 5486 |

21971 7590 02/25/2026

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# ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

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**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Alexis HOWERTON, San Francisco, CA;
Hal GERBER, San Francisco, CA;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

Spruce Biosciences, Inc., South San Francisco, CA;

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# The Director

of the United States Patent and Trademark Office has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this United States

# Patent

grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America, and if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States of America, products made by that process, for the term set forth in 35 U.S.C. 154(a)(2) or (c)(1), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b). See the Maintenance Fee Notice on the inside of the cover.

John A. Squires

Director of the United States Patent and Trademark Office

## Maintenance Fee Notice

If the application for this patent was filed on or after December 12, 1980, maintenance fees are due three years and six months, seven years and six months, and eleven years and six months after the date of this grant, or within a grace period of six months thereafter upon payment of a surcharge as provided by law. The amount, number and timing of the maintenance fees required may be changed by law or regulation. Unless payment of the applicable maintenance fee is received in the United States Patent and Trademark Office on or before the date the fee is due or within a grace period of six months thereafter, the patent will expire as of the end of such grace period.

## Patent Term Notice

If the application for this patent was filed on or after June 8, 1995, the term of this patent begins on the date on which this patent issues and ends twenty years from the filing date of the application or, if the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121, 365(c), or 386(c), twenty years from the filing date of the earliest such application ("the twenty-year term"), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b), and any extension as provided by 35 U.S.C. 154(b) or 156 or any disclaimer under 35 U.S.C. 253.

If this application was filed prior to June 8, 1995, the term of this patent begins on the date on which this patent issues and ends on the later of seventeen years from the date of the grant of this patent or the twenty-year term set forth above for patents resulting from applications filed on or after June 8, 1995, subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b) and any extension as provided by 35 U.S.C. 156 or any disclaimer under 35 U.S.C. 253.

US012569491B2

(12) **United States Patent**
**Howerton et al.**

(10) **Patent No.: US 12,569,491 B2**
(45) **Date of Patent: *Mar. 10, 2026**

(54) **METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS**

(71) Applicant: **Spruce Biosciences, Inc.**, South San Francisco, CA (US)

(72) Inventors: **Alexis Howerton**, San Francisco, CA (US); **Hal Gerber**, San Francisco, CA (US)

(73) Assignee: **SPRUCE BIOSCIENCES, INC.**, South San Francisco, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **19/043,275**

(22) Filed: **Jan. 31, 2025**

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US 2025/0177404 A1 Jun. 5, 2025

**Related U.S. Application Data**

(63) Continuation of application No. 18/941,832, filed on Nov. 8, 2024, which is a continuation of application No. 17/667,285, filed on Feb. 8, 2022, now abandoned, which is a continuation of application No. 17/081,694, filed on Oct. 27, 2020, now Pat. No. 11,304,950, which is a continuation of application No. PCT/US2019/029486, filed on Apr. 26, 2019.

(60) Provisional application No. 62/822,815, filed on Mar. 23, 2019, provisional application No. 62/663,951, filed on Apr. 27, 2018.

(51) **Int. Cl.**

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(58) **Field of Classification Search**

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See application file for complete search history.

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*Primary Examiner* — Sarah Pihonak

(74) *Attorney, Agent, or Firm* — WILSON SONSINI GOODRICH & ROSATI

(57) **ABSTRACT**

Provided herein are compounds and pharmaceutical compositions for the prevention and treatment of testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART).

**19 Claims, 14 Drawing Sheets**

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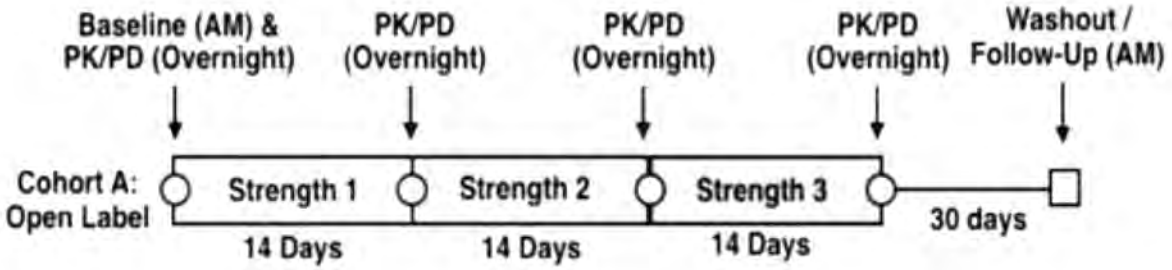

Baseline (AM) & PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
PK/PD (Overnight)
Washout / Follow-Up (AM)
Cohort A: Open Label
Strength 1
Strength 2
Strength 3
14 Days
14 Days
14 Days
30 days

*FIG. 1A*

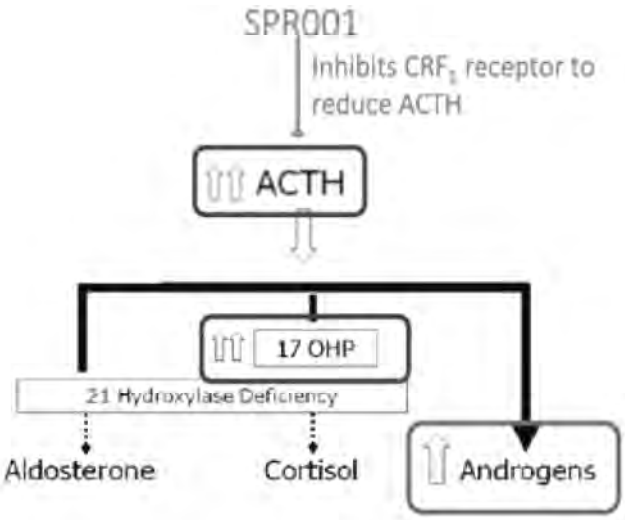

SPR001
Inhibits CRF1 receptor to reduce ACTH
ACTH
17 OHP
21 Hydroxylase Deficiency
Aldosterone
Cortisol
Androgens

*FIG. 1B*

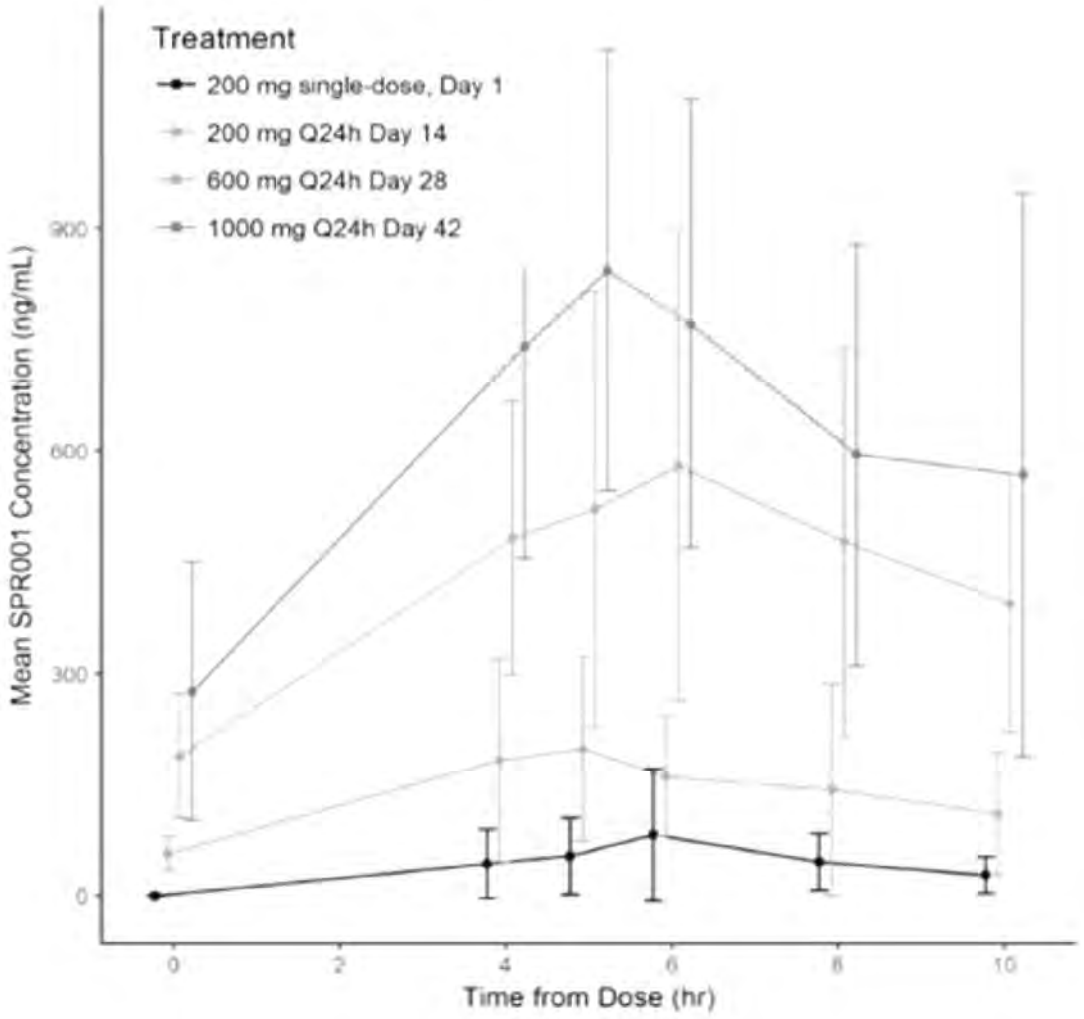

Treatment
200 mg single-dose, Day 1
200 mg Q24h Day 14
600 mg Q24h Day 28
1000 mg Q24h Day 42
Mean SPR001 Concentration (ng/mL)
900
600
300
0
0
2
4
6
8
10
Time from Dose (hr)

*FIG. 2*

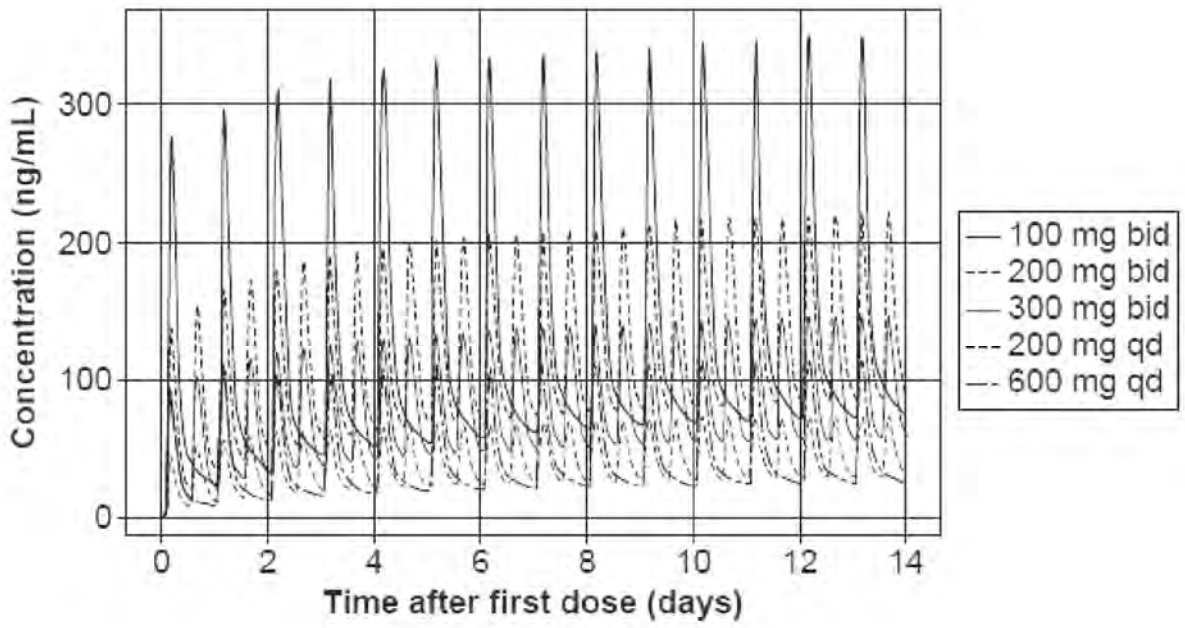

Concentration (ng/mL)
300
200
100
0
0
2
4
6
8
10
12
14
Time after first dose (days)
100 mg bid
200 mg bid
300 mg bid
200 mg qd
600 mg qd

FIG. 3

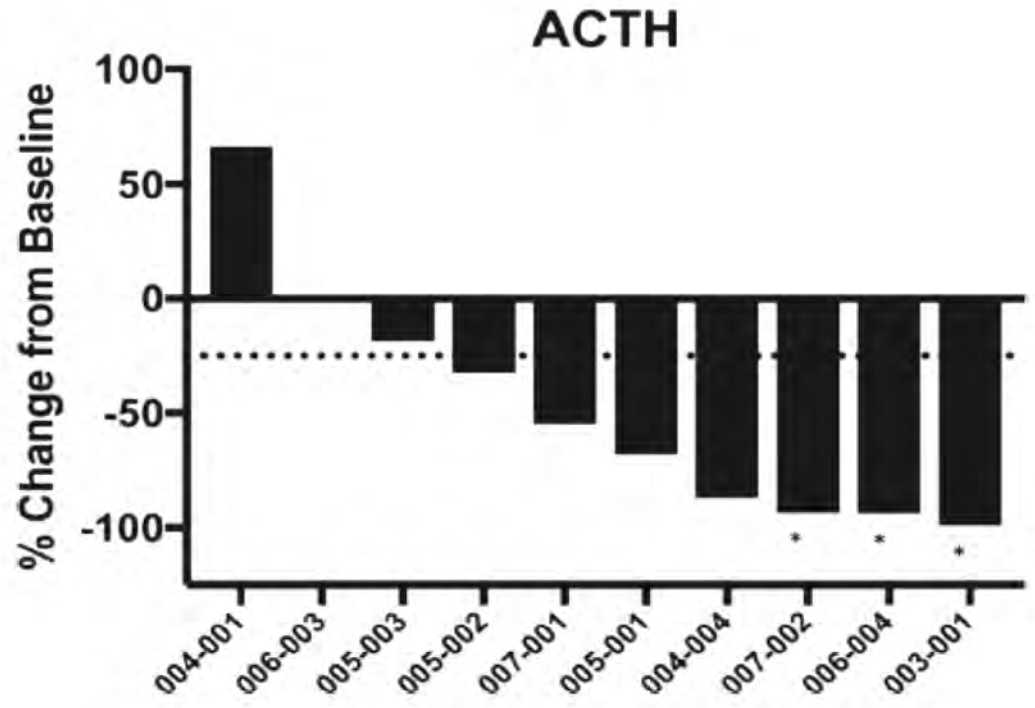

ACTH
% Change from Baseline
100
50
0
-50
-100
*
*
*
004-001
006-003
005-003
005-002
007-001
005-001
004-004
007-002
006-004
003-001

FIG. 4

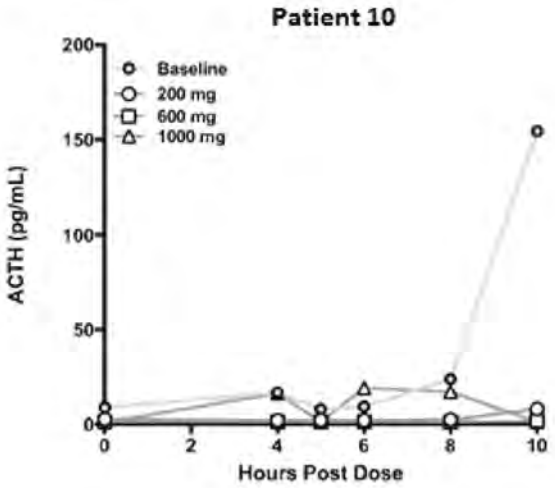



FIG. 5A

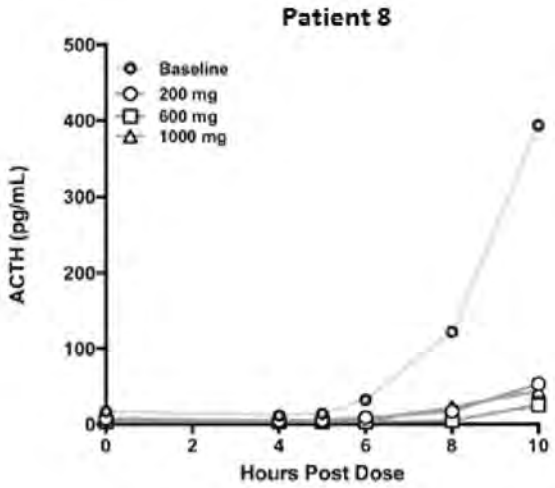



FIG. 5B

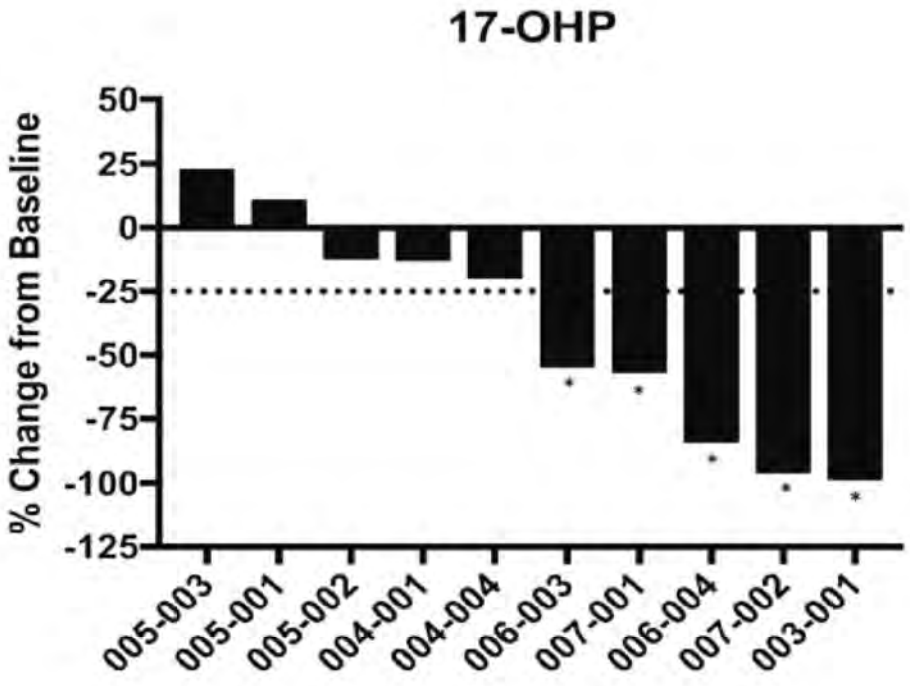



FIG. 6

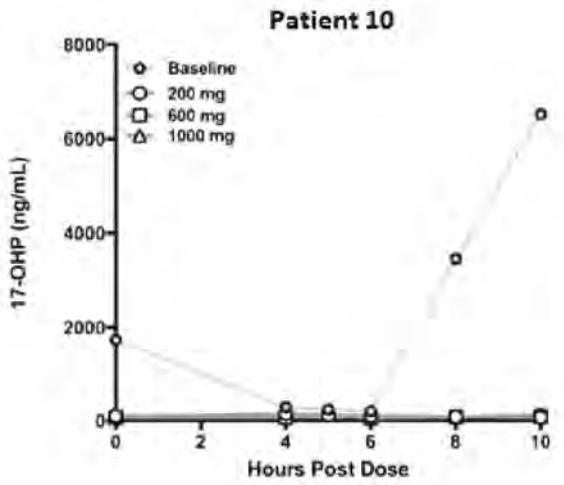



FIG. 7A

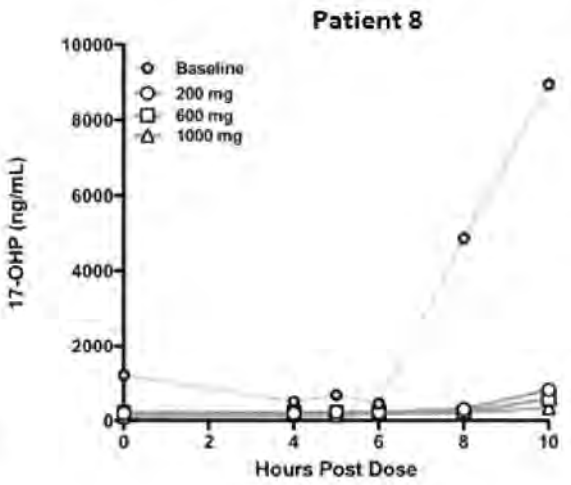



FIG. 7B

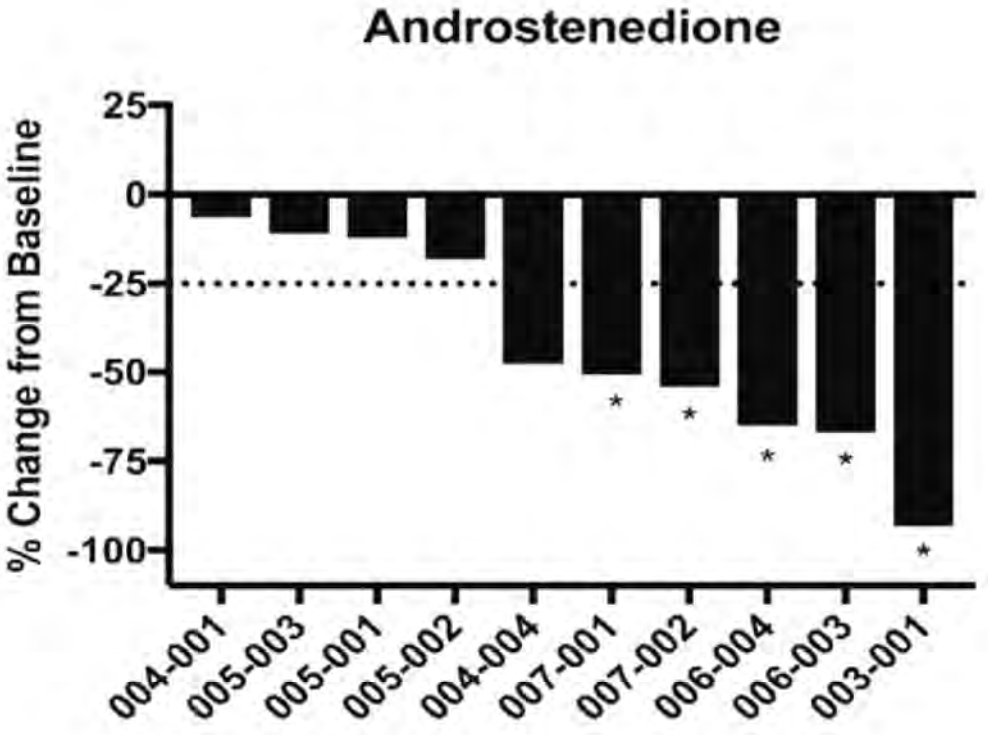



FIG. 8

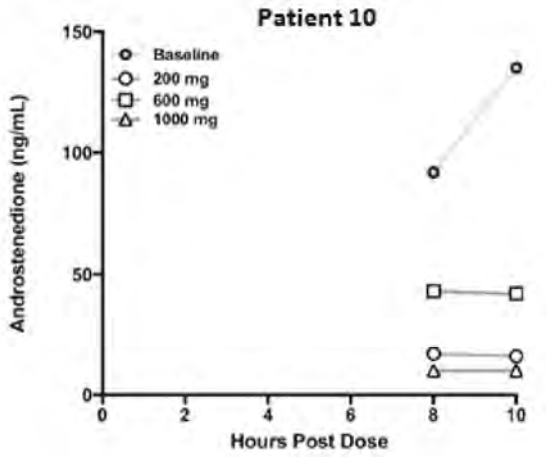



FIG. 9A

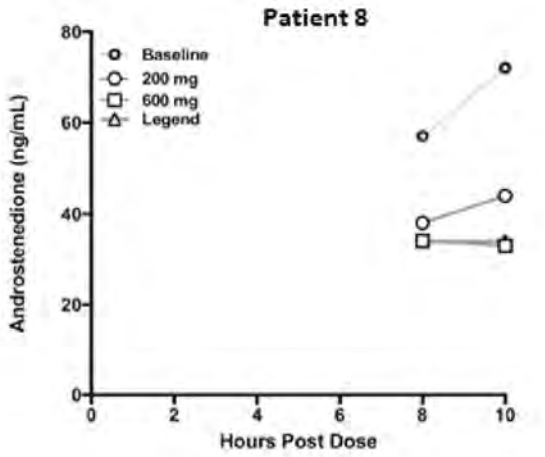



FIG. 9B

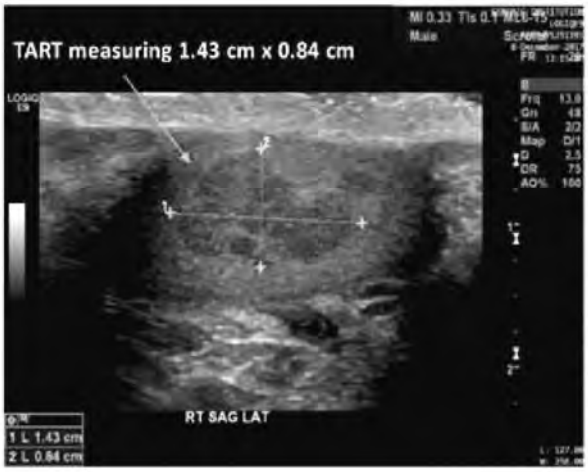



FIG. 10A

FIG. 10B

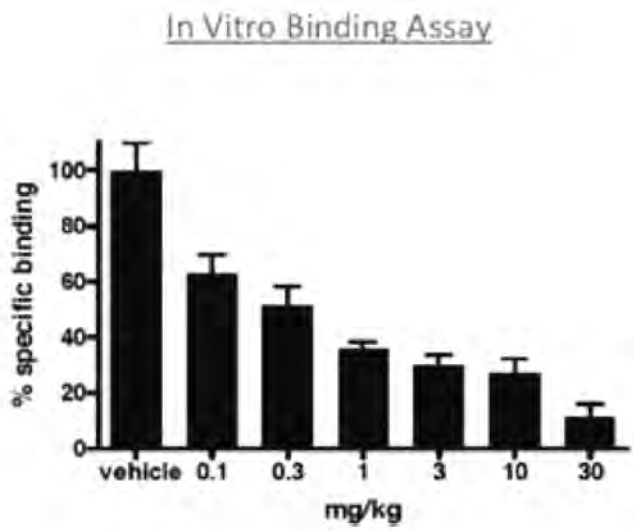



FIG. 11A

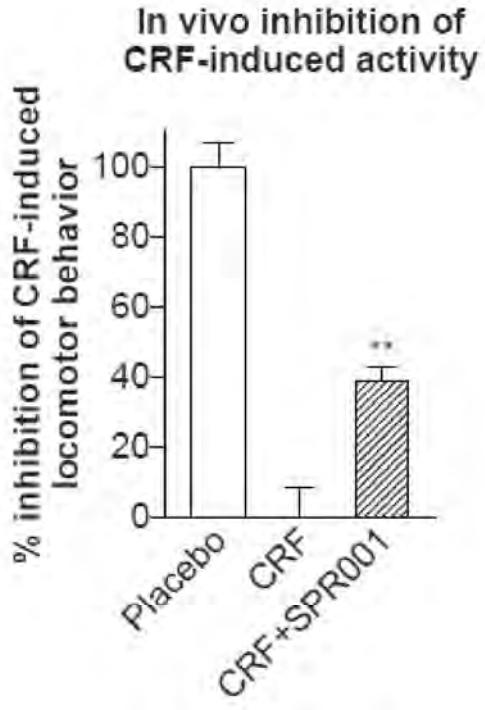



FIG. 11B

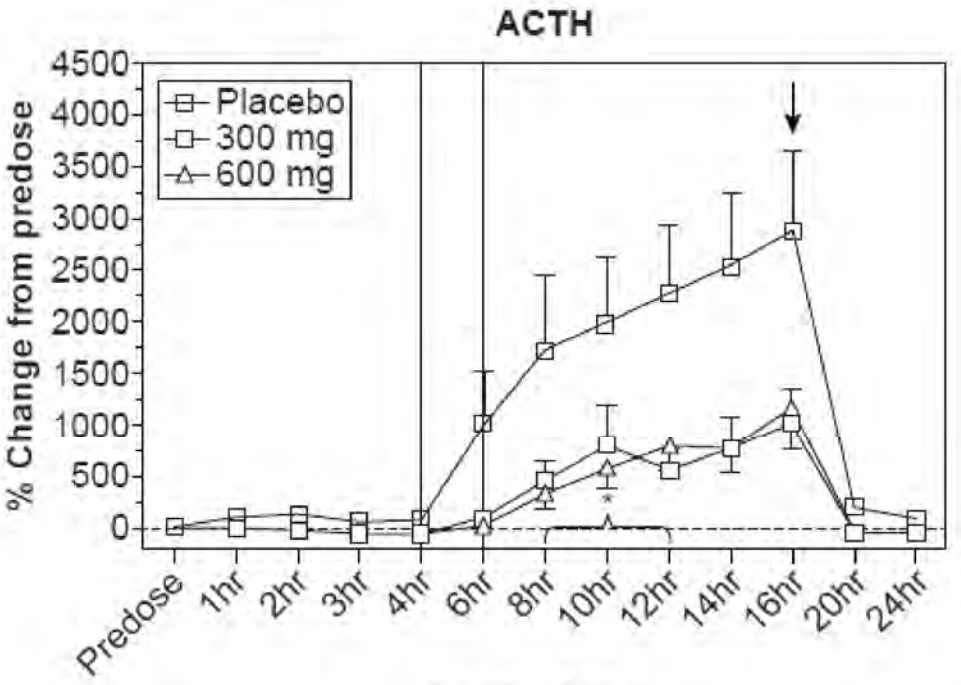



FIG. 12A

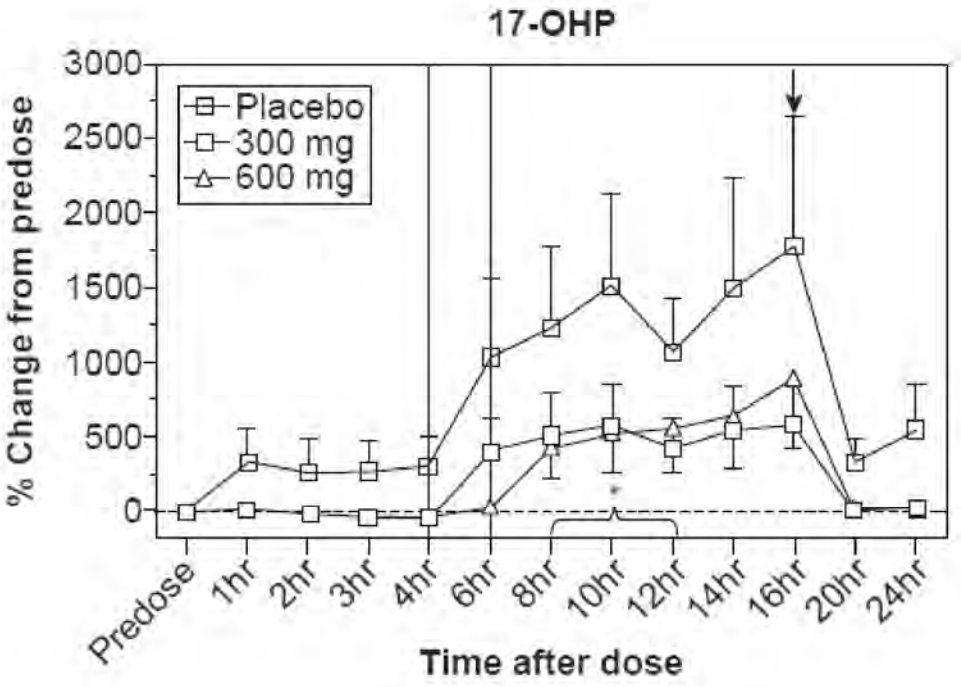



FIG. 12B

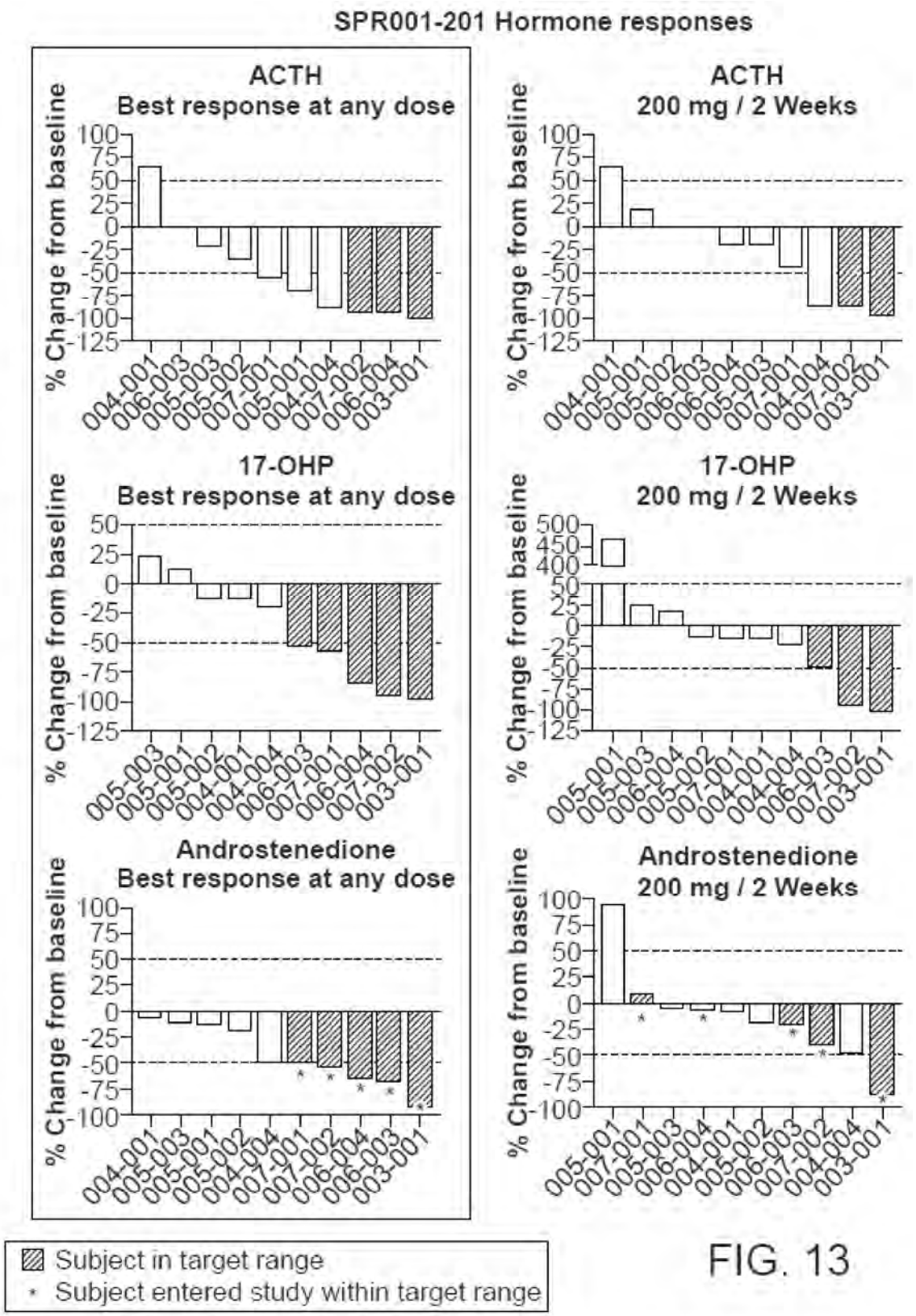



FIG. 13

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

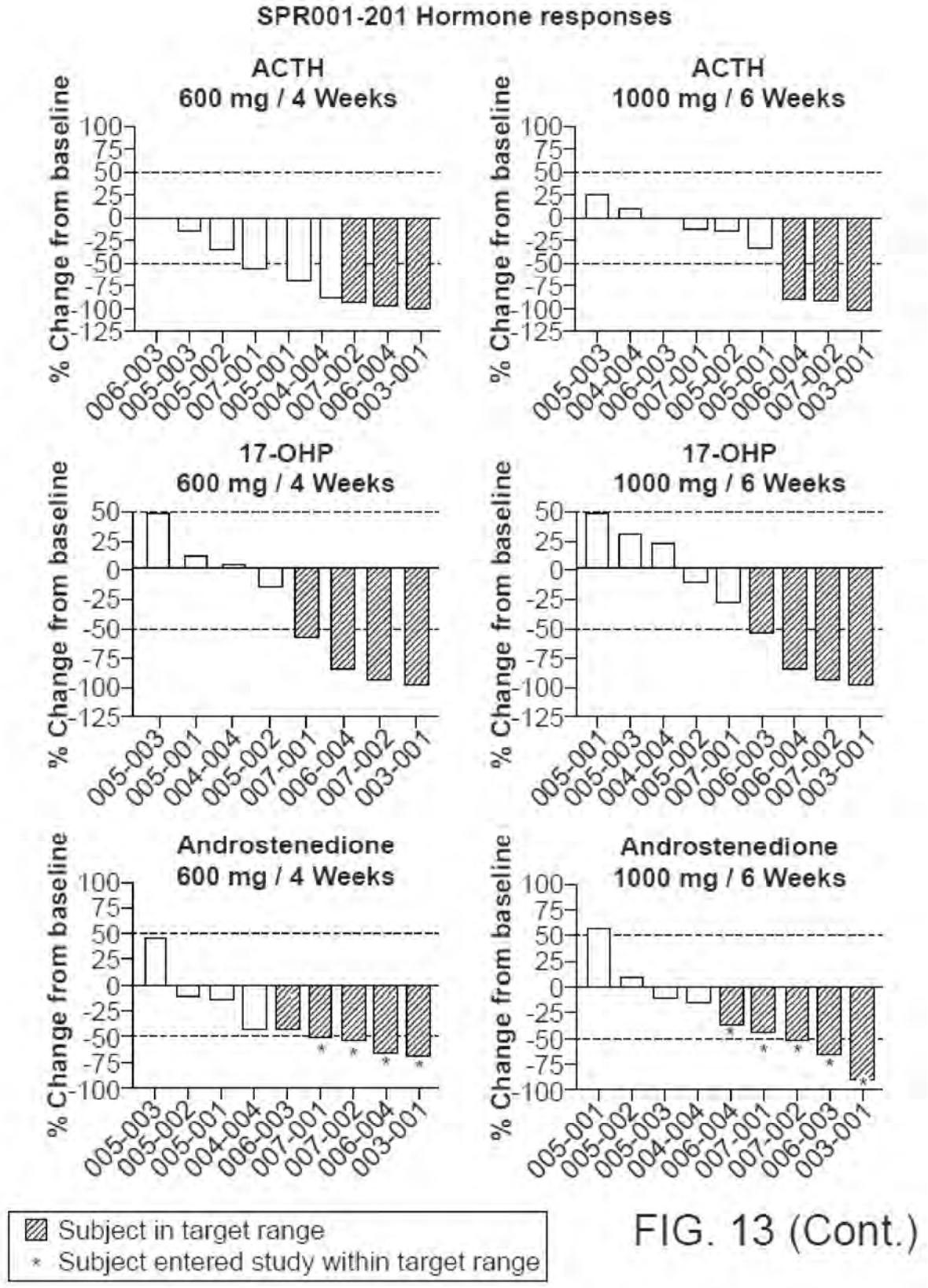



FIG. 13 (Cont.)

ACTH: 7.2-63.3 pg/mL 17-OHP: <1200 ng/dL A4: 41-262 ng/dL (M) 27-152 ng/dL (F)

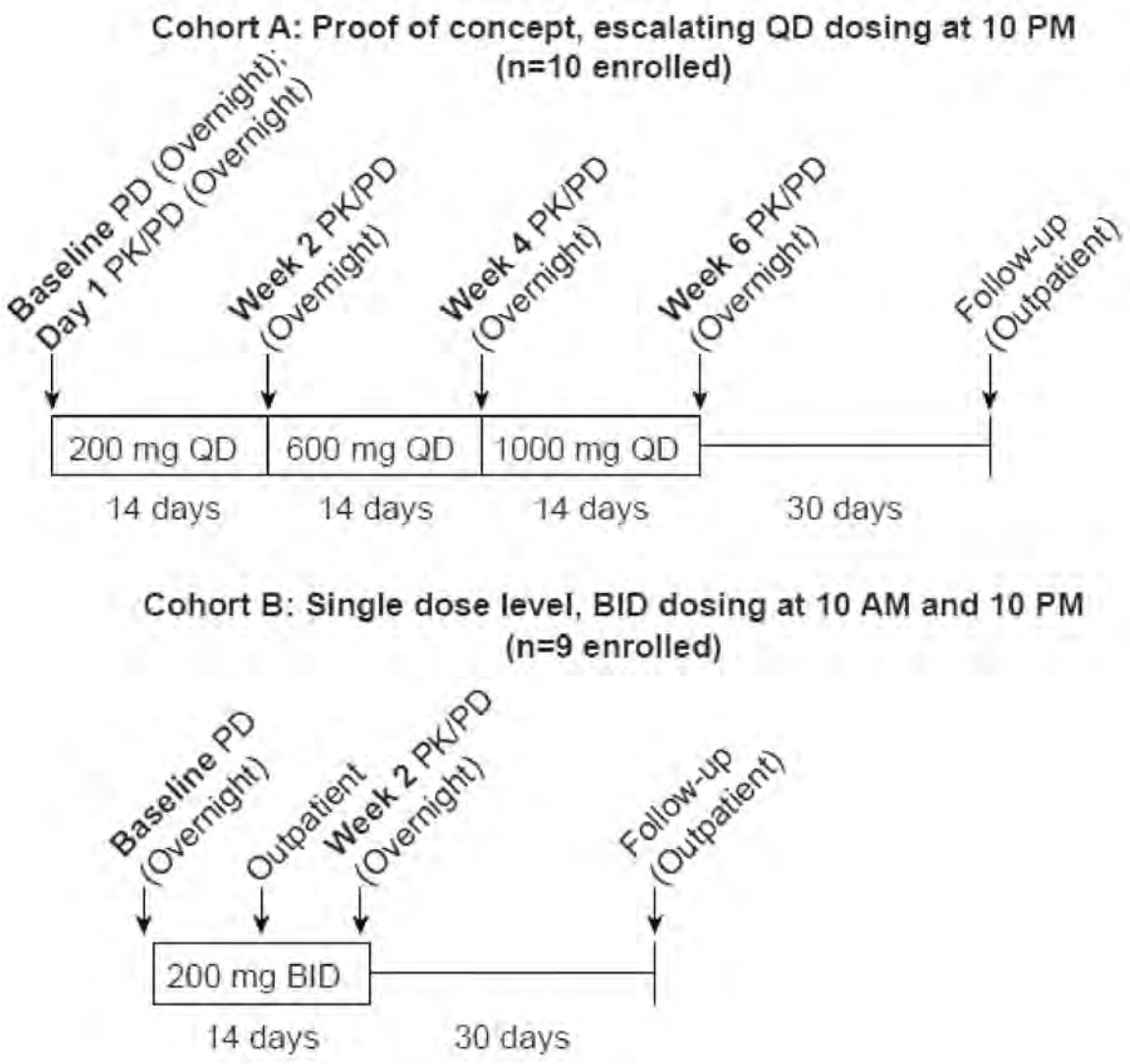

Cohort A: Proof of concept, escalating QD dosing at 10 PM
(n=10 enrolled)
Baseline PD (Overnight);
Day 1 PK/PD (Overnight)
Week 2 PK/PD
(Overnight)
Week 4 PK/PD
(Overnight)
Week 6 PK/PD
(Overnight)
Follow-up
(Outpatient)
200 mg QD
600 mg QD
1000 mg QD
14 days
14 days
14 days
30 days
Cohort B: Single dose level, BID dosing at 10 AM and 10 PM
(n=9 enrolled)
Baseline PD
(Overnight)
Outpatient
Week 2 PK/PD
(Overnight)
Follow-up
(Outpatient)
200 mg BID
14 days
30 days

FIG. 14

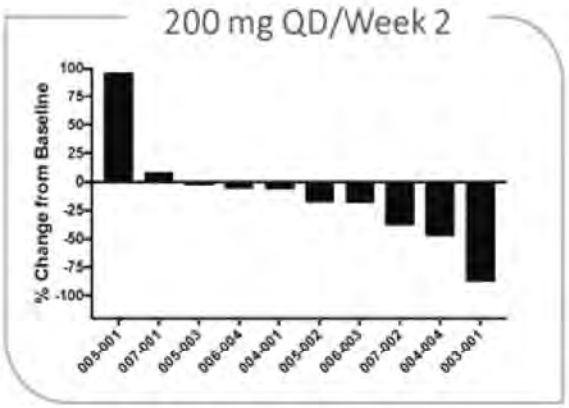



FIG. 15A

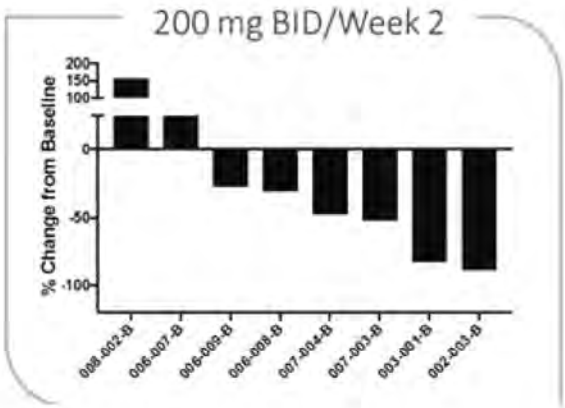



FIG. 15B

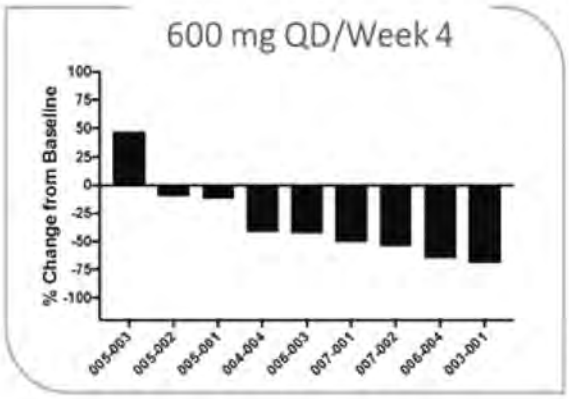



FIG. 15C

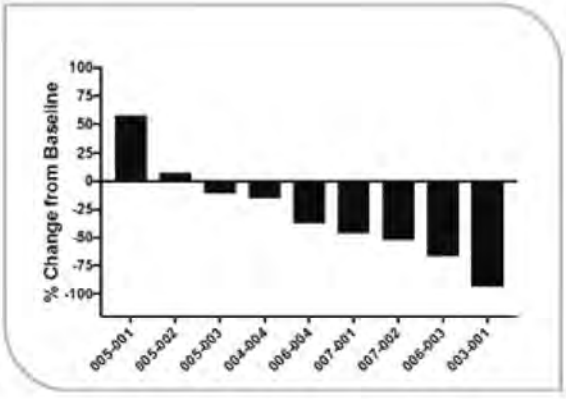



FIG. 15D

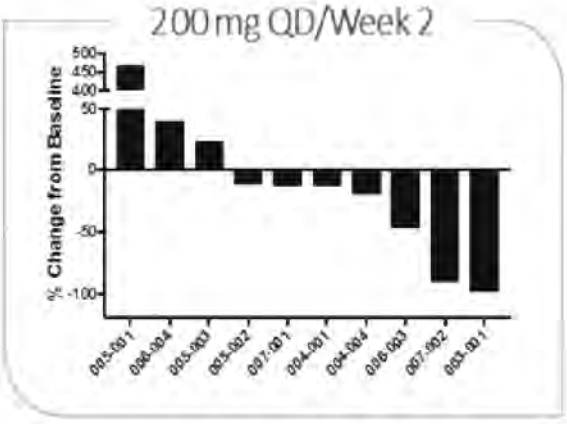



FIG. 16A

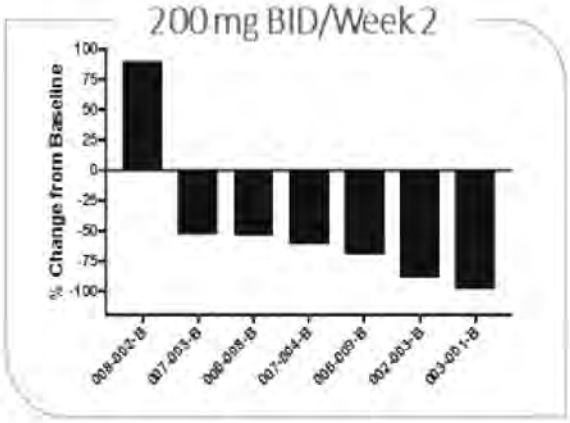



FIG. 16B

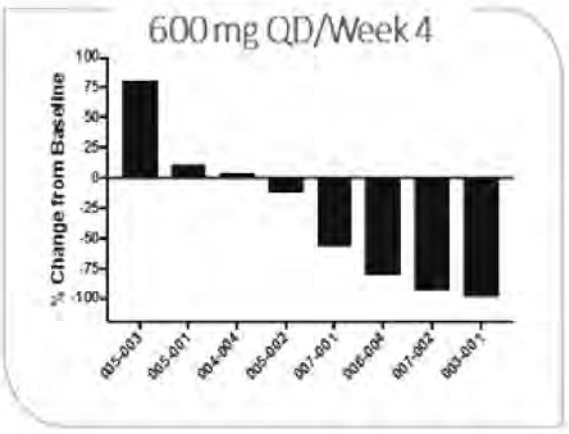



FIG. 16C

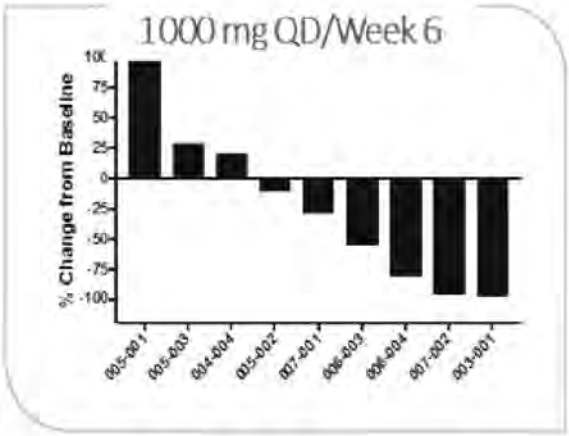



FIG. 16D

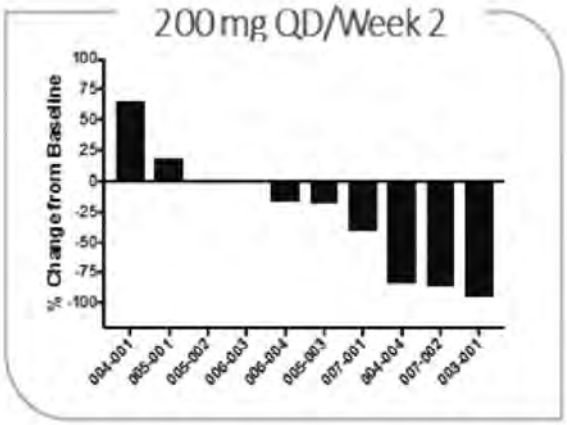



FIG. 17A

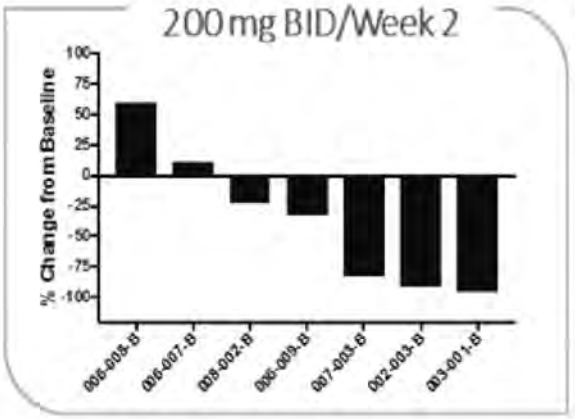



FIG. 17B

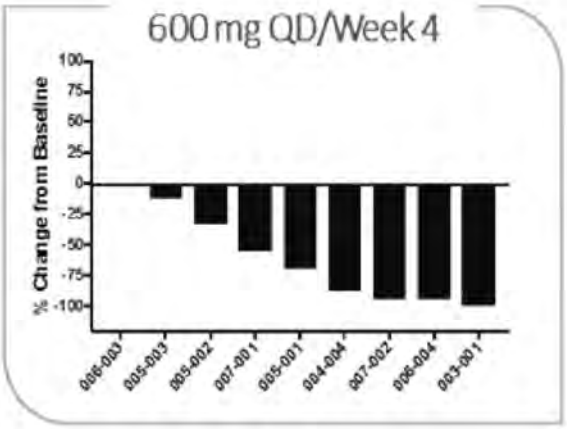



FIG. 17C

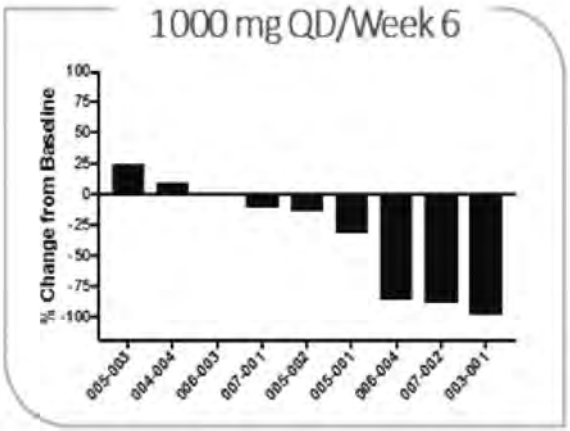



FIG. 17D

# METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

## CROSS-REFERENCE

This application is a continuation of U.S. application Ser. No. 18/941,832, filed Nov. 8, 2024, which is a continuation of U.S. application Ser. No. 17/667,285, filed on Feb. 8, 2022, which is a continuation of U.S. application Ser. No. 17/081,694 filed on Oct. 27, 2020, which issued as U.S. Pat. No. 11,304,950 on Apr. 19, 2022, and which is a continuation of International Application No. PCT/US2019/029486 filed on Apr. 26, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed Apr. 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed Mar. 23, 2019, each of which is entirely incorporated herein by reference.

## BACKGROUND

Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, inter alia, are solutions to these and other problems in the art.

## SUMMARY

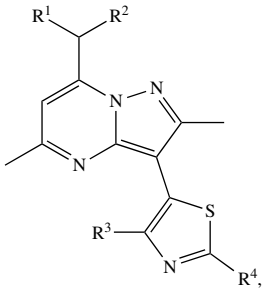
Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



(I)

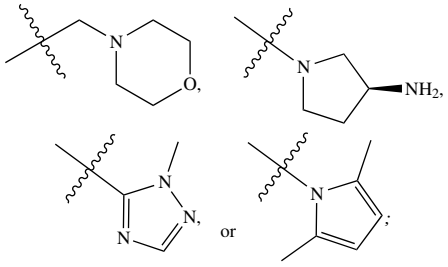
or a pharmaceutically acceptable salt thereof,

wherein:

$R^1$ and $R^2$ are independently ethyl or n-propyl;

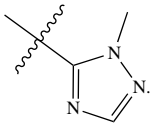
$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

$R^4$ is hydrogen, Br, $R^aR^bN$—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,

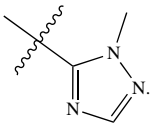


$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—.

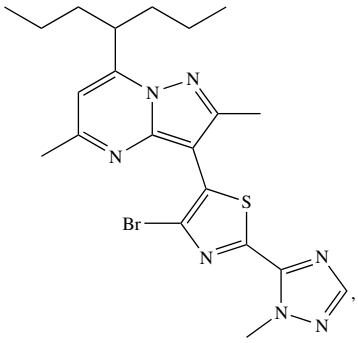
In some embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl. In some embodiments, $R^3$ is Cl, Br, or methyl. In some embodiments, $R^4$ is Br, $R^aR^bN$—, pyridin-4-yl, morpholin-4-yl, or



In some embodiments, $R^4$ is morpholin-4-yl or

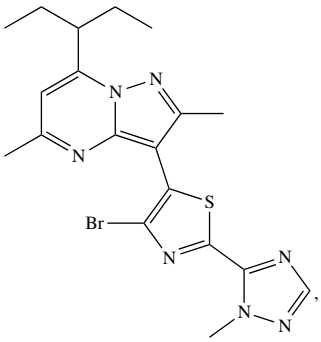


In some embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$— and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl. In some embodiments, the compound is



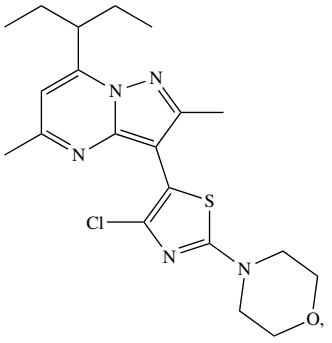
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

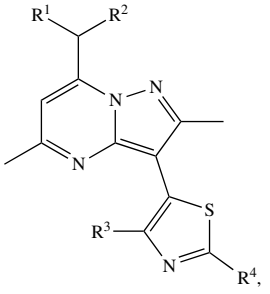
In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:

(I)



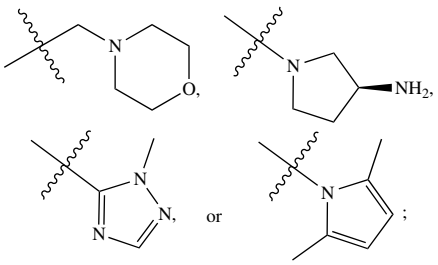
or a pharmaceutically acceptable salt thereof,

wherein:

$R^1$ and $R^2$ are independently ethyl or n-propyl;

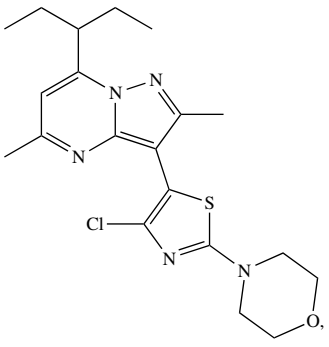
$R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

$R^4$ is hydrogen, Br, $R^aR^bN$—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—.

In some embodiments, the compound of Formula (I) has the structure:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

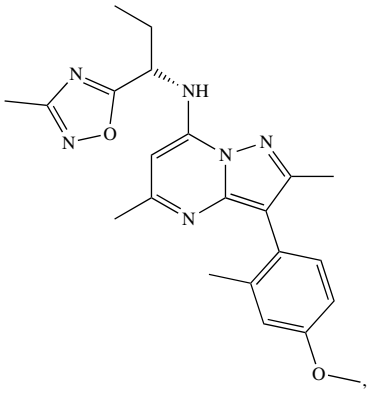
In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

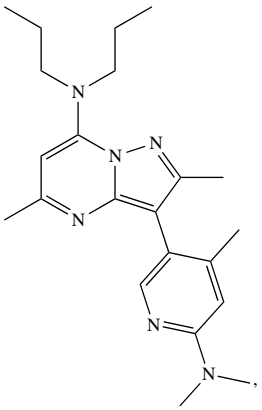
In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

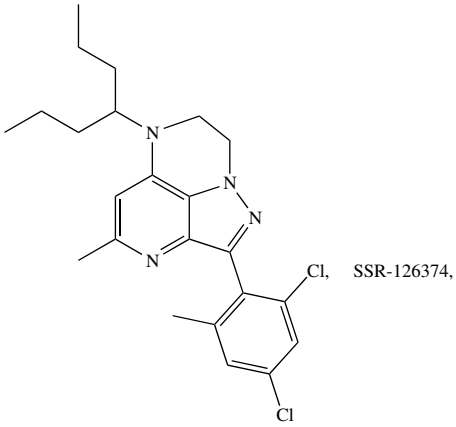
In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

In some embodiments, the additional chemotherapeutic agent is another $CRF_1$ antagonist. In some embodiments, the $CRF_1$ antagonist is







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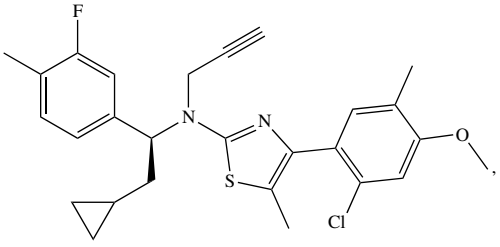

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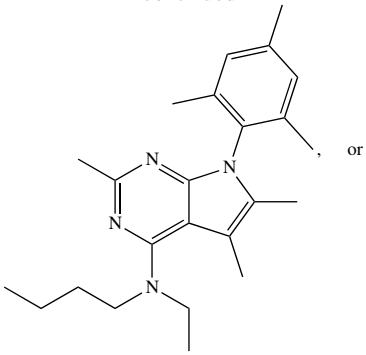
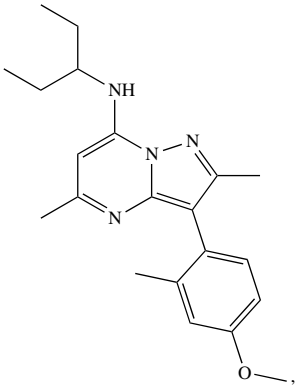
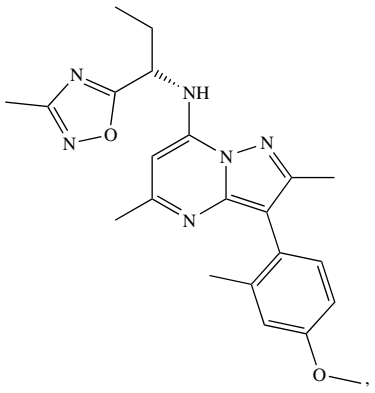


or



or a pharmaceutically acceptable salt thereof.

In some embodiments, the $CRF_1$ antagonist is



or a pharmaceutically acceptable salt thereof.

In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt

thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the $CRF_1$ antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

## INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

## BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

FIG. **1**A-**1**B. A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics (A). A schematic representation of inhibition of $CRF_1$ with a $CRF_1$ antagonist (Compound 1) (B).

FIG. **2**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a $CRF_1$ antagonist (Compound 1).

FIG. **3**. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a $CRF_1$ antagonist (Compound 1).

FIG. **4**. Graphic representation of patient-level response (measuring ACTH levels) to a $CRF_1$ antagonist (Compound 1).

FIG. **5**A-**5**B. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a $CRF_1$ antagonist [Patient 10 (A); Patient 8 (B)].

FIG. **6**. Graphic representation of patient-level response (measuring 17-OHP levels) to a $CRF_1$ antagonist (Compound 1).

FIG. **7**A-**7**B. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to a $CRF_1$ antagonist [Patient 10 (A); Patient 8 (B)].

FIG. **8**. Graphic representation of patient-level response (measuring androstenedione levels) to a $CRF_1$ antagonist (Compound 1).

FIG. **9**A-**9**B. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a $CRF_1$ antagonist (Compound 1) [Patient 10 (A); Patient 8 (B)].

FIG. **10**A-**10**B. Images of a patient with TART pre-treatment with a $CRF_1$ antagonist (Compound 1) (A) and 6-weeks post-treatment with a $CRF_1$ antagonist (Compound 1) (B).

FIG. **11**A-**11**B. Graphic representation of an in vitro binding assay of a $CRF_1$ antagonist (Compound 1); $^{125}$I-sauvagine binding to rat cerebellar membranes one hour after oral administration of increasing Compound 1 doses (A) and in vivo inhibition of CRF-induced activity after treatment with a $CRF_1$ antagonist; Compound 1 (oral, 10 mg/kg) (B).

FIG. **12**A-**12**B. Graphic representation of ACTH levels (A) and 17-OHP levels (B) after treatment with a $CRF_1$ antagonist.

FIG. **13**. Graphic representation of hormone responses after treatment with a $CRF_1$ antagonist (Compound 1).

FIG. **14** depicts the proof of concept and escalating QD dosing at 10 pm for Cohort A and the single dose level and BID dosing at 10 am and 10 pm for Cohort B.

FIG. **15**A-**15**D are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

FIG. **16**A-**16**D are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

FIG. **17**A-**17**D are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

## DETAILED DESCRIPTION

While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

I. Definitions

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that

would result from writing the structure from right to left, e.g., —$CH_2O$— is equivalent to —$OCH_2$—.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., $C_1$-$C_{10}$ means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl) methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (—O—).

The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, —$CH_2CH_2CH_2CH_2$—. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: —$CH_2$—$CH_2$—O—$CH_3$, —$CH_2$—$CH_2$—NH—$CH_3$, —$CH_2$—$CH_2$—N($CH_3$)—$CH_3$, —$CH_2$—S—$CH_2$—$CH_3$, —$CH_2$—$CH_2$, —S(O)—$CH_3$, —$CH_2$—$CH_2$—S($O)_2$—$CH_3$, —CH═CH—O—$CH_3$, —Si($CH_3)_3$, —$CH_2$—CH═N—$OCH_3$, —CH═CH—N($CH_3$)—$CH_3$, —O—$CH_3$, —O—$CH_2$—$CH_3$, and —CN. Up to two or three heteroatoms may be consecutive, such as, for example, —$CH_2$—NH—$OCH_3$ and —$CH_2$—O—Si($CH_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, —$CH_2$—$CH_2$—S—$CH_2$—$CH_2$— and —$CH_2$—S—$CH_2$—$CH_2$—NH—$CH_2$—. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula —$C(O)_2R'$— represents both —$C(O)_2R'$— and —$R'C(O)_2$—. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as —C(O)R', —C(O)NR', —NR'R", —OR', —SR', and/or —$SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as —NR'R" or the like, it will be understood that the terms heteroalkyl and —NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as —NR'R" or the like.

The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo($C_1$-$C_4$)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "acyl" means, unless otherwise stated, —C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6

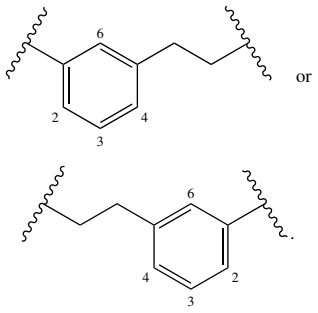
members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be —O— bonded to a ring heteroatom nitrogen.

Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

The symbol " " denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:




An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, —$N_3$, —$CF_3$, —$CCl_3$, —$CBr_3$, —$CI_3$, —CN, —CHO, —OH, —$NH_2$, —COOH, —$CONH_2$, —$NO_2$, —SH, —$SO_2CH_3$—$SO_3H$, —$OSO_3H$, —$SO_2NH_2$, —$NHNH_2$, —$ONH_2$, —NHC(O)$NHNH_2$, substituted or unsubstituted $C_1$-$C_5$ alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, —OR', =O, =NR', =N—OR', —NR'R", —SR', -halogen, —SiR'R"R'", —OC(O)R', —C(O)R', —$CO_2$R', —CONR'R", —OC(O)NR'R", —NR"C(O)R', —NR'—C(O)NR"R'", —NR"$C(O)_2$R', —NR—C(NR'R"R'")=NR"", —NR—C(NR'R")=NR'", —S(O)R', —$S(O)_2$R', —$S(O)_2$NR'R", —$NRSO_2$R', —NR'NR"R'", —ONR'R", —NR'C(O)NR"NR"R"", —CN, —$NO_2$, —$NR'SO_2$R", —NR'C(O)R", —NR'C(O)—OR", —NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R'", and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, —NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., —$CF_3$ and —$CH_2CF_3$) and acyl (e.g., —$C(O)CH_3$, —$C(O)CF_3$, —$C(O)CH_2OCH_3$, and the like).

Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: —OR', —NR'R", —SR',

-halogen, —SiR'R"R'", —OC(O)R', —C(O)R', —$CO_2$R', —CONR'R", —OC(O)NR'R", —NR"C(O)R', —NR'—C(O)NR"R'", —NR"$C(O)_2$R', —NR—C(NR'R"R'")═NR"", —NR—C(NR'R")═NR'", —S(O)R', —$S(O)_2$R', —$S(O)_2$NR'R", —$NRSO_2$R', —NR'NR"R'", —ONR'R", —NR'C(O)NR"NR'"R"", —CN, —$NO_2$, —R', —$N_3$, —$CH(Ph)_2$, fluoro($C_1$-$C_4$)alkoxy, and fluoro($C_1$-$C_4$)alkyl, —NR'$SO_2$R", —NR'C(O)R", —NR'C(O)—OR", —NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R'", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" groups when more than one of these groups is present.

Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)—$(CRR')_q$—U—, wherein T and U are independently —NR—, —O—, —CRR'—, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$—B—, wherein A and B are independently —CRR'—, —O—, —NR—, —S—, —S(O)—, —$S(O)_2$—, —$S(O)_2$NR'—, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula —$(CRR')_s$—X'—$(C"R"R'")_d$—, where s and d are independently integers of from 0 to 3, and X is —O—, —NR'—, —S—, —S(O)—, —$S(O)_2$—, or —$S(O)_2$NR'—. The substituents R, R', R", and R'" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, —$CF_3$, —CN, —OH, —$NH_2$, —COOH, —$CONH_2$, —$NO_2$, —SH, —$SO_3H$, —$SO_4H$, —$SO_2NH_2$, —$NHNH_2$, —$ONH_2$, —NHC═(O)$NHNH_2$, —NHC═(O)$NH_2$, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —$OCF_3$, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, —$CF_3$, —CN, —OH, —$NH_2$, —COOH, —$CONH_2$, —$NO_2$, —SH, —$SO_3H$, —$SO_4H$, —$SO_2NH_2$, —$NHNH_2$, —$ONH_2$, —NHC═(O)$NHNH_2$, —NHC═(O)$NH_2$, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —$OCF_3$, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, —$CF_3$, —CN, —OH, —$NH_2$, —COOH, —$CONH_2$, —$NO_2$, —SH, —$SO_3H$, —$SO_4H$, —$SO_2NH_2$, —$NHNH_2$, —$ONH_2$, —NHC═(O)$NHNH_2$, —NHC═(O)$NH_2$, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —$OCF_3$, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one sub-

stituent selected from: oxo, halogen, —$CF_3$, —CN, —OH, —$NH_2$, —COOH, —$CONH_2$, —$NO_2$, —SH, —$SO_3H$, —$SO_4H$, —$SO_2NH_2$, —$NHNH_2$, —$ONH_2$, —NHC═(O)$NHNH_2$, —NHC═(O)$NH_2$, —$NHSO_2H$, —NHC═(O)H, —NHC(O)—OH, —NHOH, —$OCF_3$, —$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

A "size-limited substituent" or "size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_{20}$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_8$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

A "lower substituent" or "lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_8$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted $C_1$-$C_{20}$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_8$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted $C_1$-$C_{20}$ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted $C_3$-$C_8$ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted $C_6$-$C_{10}$ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted $C_1$-$C_8$ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted $C_3$-$C_7$ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted $C_6$-$C_{10}$ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted $C_1$-$C_8$ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted $C_3$-$C_7$ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted $C_6$-$C_{10}$ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as

enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by $^{13}C$- or $^{14}C$-enriched carbon are within the scope of this invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium ($^{3}H$), iodine-125 ($^{125}I$), or carbon-14 ($^{14}C$). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

"Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted $C_1$-$C_{20}$ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted $C_1$-$C_{20}$ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple $R^{13}$ substituents are present, each $R^{13}$ substituent may be distinguished as $R^{13A}$, $R^{13B}$, $R^{13C}$, $R^{13D}$, etc., wherein each of $R^{13A}$, $R^{13B}$, $R^{13C}$, $R^{13D}$, etc. is defined within the scope of the definition of $R^{13}$ and optionally differently.

A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radiolabeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", *Journal of Pharmaceutical Science,* 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (−)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted in vivo after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

"Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of a compound to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and "protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (e.g. non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, e.g., in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed in vitro or in vivo from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

"Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist. In embodiments, an agonist is a molecule that

interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

The terms "corticotropin-releasing factor type-1," "$CRF_1$," "corticotropin-releasing hormone receptor 1," and "CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms include any recombinant or naturally-occurring form of $CRF_1$ variants thereof that maintain $CRF_1$ activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of $CRF_1$ variants (e.g., frameshift mutations) thereof that maintain $CRF_1$ activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype $CRF_1$). In embodiments, the $CRF_1$ protein encoded by the CRHR1 gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (e.g., ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, etc.).

The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (e.g., Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

"Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

"Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma *cutaneum*, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatinifomi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma *mucosum*, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma *tuberosum*, tuberous carcinoma, verrucous carcinoma, or carcinoma *villosum.*

The terms "treating" or "treatment" refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-

being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

"Treating" or "treatment" as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (i.e., not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (e.g., ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

"Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

"Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

An "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy,* 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a CRF1 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically

effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

The terms "QD," "qd," and "q.d." refer to once a day, i.e., a drug or therapeutic agent is administered once a day for the duration of the therapeutic regimen.

The terms "BD," "bd," and "b.i.d." refer to twice a day, i.e., a drug or therapeutic agent is administered two times a day for the duration of the therapeutic regimen.

The terms "QID," "qid," and "q.i.d." refer to three times a day, i.e., a drug or therapeutic agent is administered three times a day for the duration of the therapeutic regimen.

Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc. By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym*. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., *Gao Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, e.g., Al-Muhammed, *J Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each

other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

The compounds described herein can be administered to treat a fertility disease or disorder and/or cancer. In this regard, the compounds disclosed herein may be administered either alone to treat such diseases or disorders or may be co-administered with another therapeutic agent to treat such diseases or disorders.

The compounds disclosed herein may be co-administered with an agonist or antagonist of $CRF_1$ function. The compounds described herein can be co-administered with conventional anti-cancer/chemotherapeutic.

"Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/AZD6244, GSK1120212/trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (e.g., 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, etc.), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, etc.), platinum-based compounds (e.g. cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; daclixiimab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofyl-

line; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including recombinant interleukin II, or rlL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.™ (i.e. paclitaxel), Taxotere.™, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5,

Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta *Medica*), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, lnanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta *Medica*), D-68144 (Asta *Medica*), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (−)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta *Medica*), D-68836 (Asta *Medica*), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., *Bacillus* Calmette-Guerin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-*pseudomonas* exotoxin conjugate, etc.), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to $^{111}$In, $^{90}$Y, or $^{131}$I, etc.), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa™) erlotinib (Tarceva™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™) vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

"Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

The compounds disclosed herein may be co-administered with an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a *vinca* alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5.alpha.-reductase such as finasteride; (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoli-n-4-amine (gefitinib, AZD 1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazoli-n-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family; (v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for

example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin .alpha.v.beta.3 function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

In embodiments, the compounds disclosed herein can be co-administered with an antibody, such as a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax 11-15) or antibody modulating Ig function such as anti-IgE (for example omalizumab).

In embodiments, treatment of cancer includes administration of an effective amount of at least two of the following: a CRF1 inhibitor, an inhibitor of the PD-L1/PD-1 pathway, an inhibitor of CTLA-4, an agonistic antibody of CD137 (4-1BB). In some embodiments, the method may comprise the use of two or more combinations.

In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as $^{47}Sc$, $^{64}Cu$, $^{67}Cu$, $^{89}Sr$, $^{86}Y$, $^{87}Y$, $^{90}Y$, $^{105}Rh$, $^{111}Ag$, $^{111}In$, $^{117m}Sn$, $^{149}Pm$, $^{153}Sm$, $^{166}Ho$, $^{177}Lu$, $^{186}Re$, $^{188}Re$, $^{211}At$, and $^{212}Bi$, optionally conjugated to antibodies directed against tumor antigens.

In addition, a $CRF_1$ inhibitor may be combined with the therapeutic administration of immune cells, sometimes referred to as adoptive cell transfer. These cells may be cells from the patient, a genetically related or unrelated donor, they may be genetically modified (e.g. CAR-T cells, NK cells, etc), cell lines, genetically modified cell lines and live or dead versions of the above. CRF1 inhibitors may also be combined with vaccines of any kind (e.g. protein/peptide, viral, bacterial, cellular) to stimulate immune responses to cancer.

The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein may be administered once daily until study reached endpoint. The $CRF_1$ inhibitors/$CRF_1$ antagonists disclosed herein may be administered at least three times but in some studies four or more times depending on the length of the study and/or the design of the study.

The methods disclosed herein may be used in combination with additional cancer therapy. In some embodiments, the distinct cancer therapy comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy. In some embodiments, the cancer is a chemotherapy-resistant or radio-resistant cancer.

A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (e.g., *spodoptera*) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

"Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. In some embodiments, a CRF1 associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with $CRF_1$ (e.g. an endocrine disorder, a cancer including but not limited to TART or OART). A $CRF_1$ modulator is a compound that increases or decreases the activity or function or level of activity or level of function of $CRF_1$. A modulator may act alone, or it may use a cofactor, e.g., a protein, metal ion, or small molecule. Examples of modu-

lators include small molecule compounds and other bioorganic molecules. Numerous libraries of small molecule compounds (e.g., combinatorial libraries) are commercially available and can serve as a starting point for identifying a modulator. The skilled artisan is able to develop one or more assays (e.g., biochemical or cell-based assays) in which such compound libraries can be screened in order to identify one or more compounds having the desired properties; thereafter, the skilled medicinal chemist is able to optimize such one or more compounds by, for example, synthesizing and evaluating analogs and derivatives thereof. Synthetic and/or molecular modeling studies can also be utilized in the identification of an activator.

The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms "modulate", "modulation" and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of $CRF_1$, either directly or indirectly, relative to the absence of the molecule.

The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, an endocrine disorder, a disease associated with $CRF_1$ activity, a $CRF_1$ associated disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, an endocrine disorder associated with $CRF_1$ activity or function may be an endocrine disorder that results (entirely or partially) from aberrant $CRF_1$ function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or an endocrine disorder wherein a particular symptom of the disease is caused (entirely or partially) by aberrant $CRF_1$ activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, an endocrine disorder associated with $CRF_1$ activity or function or a $CRF_1$ associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., $CRF_1$ modulator, $CRF_1$ inhibitor, or $CRF_1$ antagonist), in the instance where increased $CRF_1$ activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART). For example, an endocrine disorder associated with $CRF_1$ activity or function or a $CRF_1$ associated endocrine disorder, may be treated with an $CRF_1$ modulator or $CRF_1$ inhibitor, in the instance where increased $CRF_1$ activity or function (e.g. signaling pathway activity) causes the disease.

The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extracellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propogated to other signaling pathway components. For example, binding of a $CRF_1$ with a compound as described herein may reduce the level of a product of the $CRF_1$ catalyzed reaction or the level of a downstream derivative of the product or binding may reduce the interactions between the $CRF_1$ or a reaction product and downstream effectors or signaling pathway components (e.g., MAP kinase pathway), resulting in changes in cell growth, proliferation, or survival.

As used herein, the terms "corticotropin-releasing factor type-1," "$CRF_1$," "corticotropin-releasing hormone receptor 1," and "CHHR1" and all other related art-accepted terms, many of which are set forth below, refer to a compound capable of modulating, either directly or indirectly, the $CRF_1$ receptor in an in vitro assay, an in vivo model, and/or other means indicative of therapeutic efficacy. The terms also refer to a compound that exhibits at least some therapeutic benefit in a human subject.

The phrase "in a sufficient amount to effect a change" means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject's feeling of well-being).

The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

"Substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

The terms "specifically binds" and "selectively binds," when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample. The antibody, or binding composition derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen, or a variant or mutein thereof, with an affinity that is at least two-fold greater, at least 10-times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antibody, or binding composition derived therefrom. In embodiments, the antibody will have an affinity that is greater than about $10^9$ liters/mol, as determined by, e.g., Scatchard analysis (Munsen, et al. (1980) Analyt. Biochem. 107:220-239).

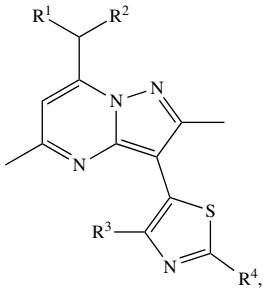
The terms "DNA," "nucleic acid," "nucleic acid molecule," "polynucleotide" and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, messenger RNA (mRNA), complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced (e.g., muteins); for example, the change is generated in the laboratory by human intervention ("hand of man"). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

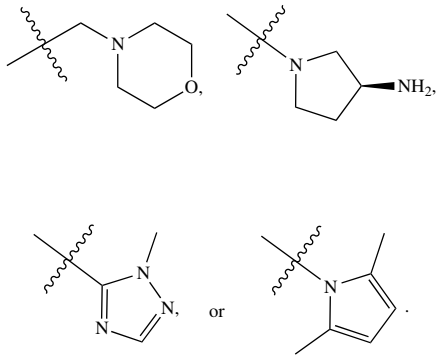
The term "muteins" as used herein refers broadly to mutated recombinant proteins. These proteins usually carry single or multiple amino acid substitutions and are frequently derived from cloned genes that have been subjected to site-directed or random mutagenesis, or from completely synthetic genes.

II. Compounds

In an aspect provided herein, is a compound of Formula (I):



or a pharmaceutically acceptable salt thereof. $R^1$ and $R^2$ are independently ethyl or n-propyl. $R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. $R^4$ is hydrogen, Br, $R^aR^bN$—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,

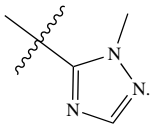


$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—In embodiments, the inhibitor forms an irreversible bond with the amino acid residue. In embodiments, the bond is a covalent bond.

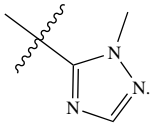
In certain embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl.

In certain embodiments, $R^3$ is Cl, Br, or methyl.

In certain embodiments, $R^4$ is Br, $R^aR^bN$—, pyridin-4-yl, morpholin-4-yl, or

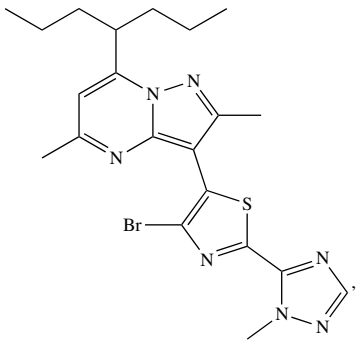


In certain embodiments, $R^4$ is morpholin-4-yl or



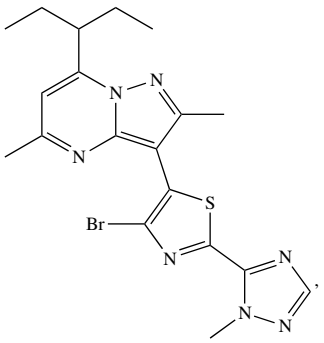
In certain embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$— and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

In certain embodiments, the compound is



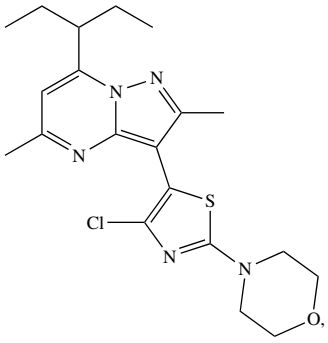
or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In one aspect described herein, there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof; and repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of said astressin.

In one aspect described herein, there is a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

In one aspect described herein, there is a method of improving quality of life in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

III. Pharmaceutical Compositions

In an aspect, there is provided a pharmaceutical composition, including a compound as described herein, including embodiments, or the structural Formula (I), and a pharmaceutically acceptable excipient.

The compounds (e.g., $CRF_1$ inhibitors/antagonists) of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are "pharmaceutical compositions" comprising a compound (e.g., $CRF_1$ inhibitor(s)/antagonist(s)) and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In certain embodiments, the compound (e.g., $CRF_1$ inhibitor/antagonist) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the pharmaceutical compositions can be administered ex vivo or in vivo to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

In one aspect described herein, there is a pharmaceutical composition in the form of a capsule comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a pharmaceutical composition in the form of a tablet comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of $CRF_1$ function) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

The tablets, capsules and the like suitable for oral administration may be uncoated or coated to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may

be employed. They may also be coated to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly (methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example *arachis* oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or *arachis* oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions typically comprise a therapeutically effective amount of a $CRF_1$ inhibitor/antagonist contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a $CRF_1$ inhibitor/antagonist, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., $CRF_1$ inhibitor/antagonist) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

The present disclosure contemplates the administration of the compound (e.g., $CRF_1$ inhibitor/antagonist) in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

The compound (e.g., $CRF_1$ inhibitor/antagonist) contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

IV. Methods

In certain embodiments, provided herein are methods for treating or preventing a disease comprising administering an effective amount of a compound of Formula (I), or an isotopic variant thereof or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In one embodiment, provided herein are methods for treating or preventing a tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a benign tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a malignant tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal rest tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In one embodiment, provided herein are methods for treating or preventing infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing male infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm count, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm motility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm morphology, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing female infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In one embodiment, provided herein are methods for treating or preventing a proliferative or hyperproliferative disease or disorder, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a cancer of the breast, skin, prostate, cervix, uterus, ovary, testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system.

In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenstrom's macroglobulinemia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain

stem glioma, ependymoma, aligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mutinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prol actin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonserninoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but not limited to, renal cell cancer, adenocarcinoma, hypemephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (See Fishman et al., 1985, *Medicine,* 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy et al., 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

Depending on the disorder, disease, or condition to be treated, and the subject's condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration as described elsewhere herein.

The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. Recommended routes of administration for the second active agents are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

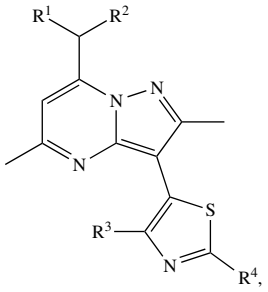
In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

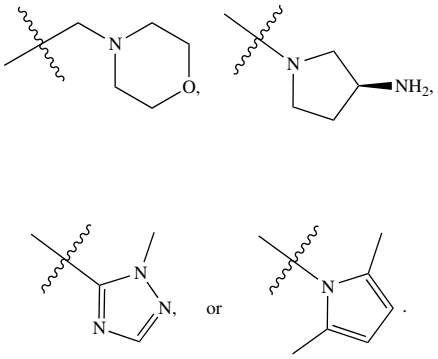
In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 ($CRF_1$) antagonist or a pharmaceutically acceptable salt thereof.

In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):

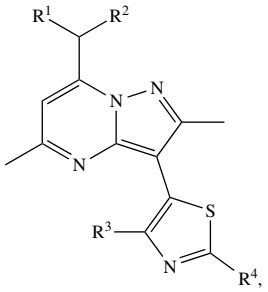


or a pharmaceutically acceptable salt thereof. $R^1$ and $R^2$ are independently ethyl or n-propyl. $R^3$ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. $R^4$ is hydrogen, Br, $R^aR^bN$—, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



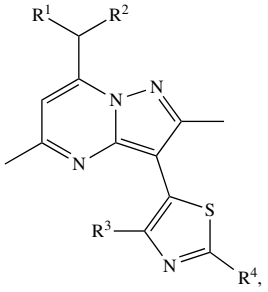
$R^a$ and $R^b$ are independently hydrogen, $C_1$-$C_3$alkyl, $H_2NCH_2CH_2$—, $(CH_3)_3COC(O)NHCH_2CH_2$—, or $CH_3CH_2CH_2NHCH_2CH_2$—.

In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments.

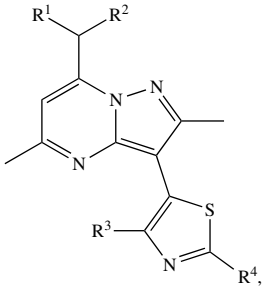
In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 60% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 70% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 80% of the subjects demonstrate reduction in ACTH. In embodiments, at least about 10% of subjects were in the standard or normal range for ACTH after treatment.

In embodiments, at least about 20% of subjects were in the standard or normal range for ACTH after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for ACTH after treatment. In certain embodiments, ACTH levels are decreased or reduced within about 30 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 1 hour post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

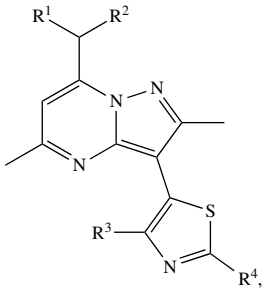
In an aspect provided herein, is a method of decreasing or reducing 17α-hydroxyprogesterone (17-OHP) levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 60% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 70% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 80% of the subjects demonstrate reduction in 17-OHP. In embodiments, at least about 30% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about

40% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 60% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 60% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment.

In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

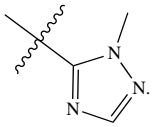


or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. $R^1$, $R^2$, $R^3$ and $R^4$ are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 60% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 70% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 80% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 90% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least 100% of the subjects demonstrate reduction in androstenedione. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least 60% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range for androstenedione after treatment.

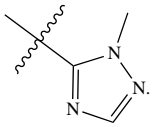
In certain embodiments, $R^3$ is Cl, Br, methyl, or trifluoromethyl.

In certain embodiments, $R^3$ is Cl, Br, or methyl.

In certain embodiments, $R^4$ is Br, $R^aR^bN$—, pyridin-4-yl, morpholin-4-yl, or

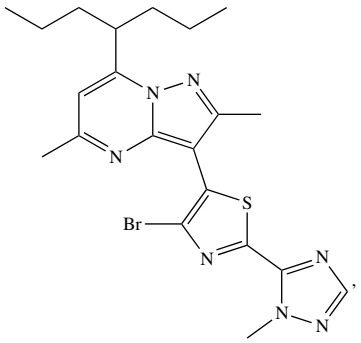


In certain embodiments, $R^4$ is morpholin-4-yl or



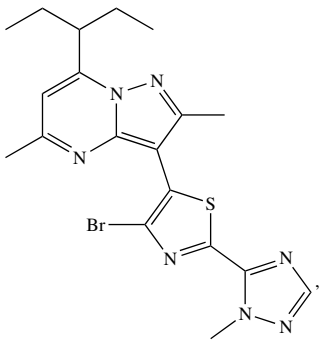
In certain embodiments, $R^4$ is hydrogen, Br, $R^aR^bN$— and $R^a$ and $R^b$ are independently $C_1$-$C_3$alkyl.

In certain embodiments, the compound is



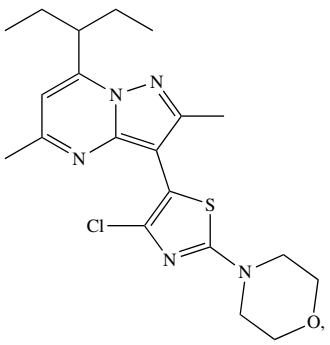
or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

In certain embodiments, a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is cyclically administered to a patient. Cycling therapy involves the administration of an active agent or a combination of active agents for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

In certain embodiments, in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein (e.g., treatment or prevention of testicular adrenal rest tumors (TART) or treatment or prevention of ovarian adrenal rest tumors (OART)), an appropriate dosage level of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof generally is ranging from about 1 mg to 3000 mg, from about 1 mg to 2000 mg, from about 1 mg to 1000 mg, from about 1 mg to about 500 mg, from about 5 mg to about 500 mg, from about 5 mg to about 400 mg, from about 5 mg to about 300 mg, from about 5 mg to about 250 mg, from about 5 mg to about 200 mg, from about 50 mg to about 200 mg, from about 10 mg to about 400 mg, from about 5 mg to about 25 mg, from about 10 mg to about 25 mg, or from about 25 to about 200 mg, which can be administered in single or multiple doses. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg/day.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable

salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, or about 1000 mg.

For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing from about 1.0 mg to about 1,000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465

mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof for the symptomatic adjustment of the dosage to the patient to be treated. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 50 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 200 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. The pharmaceutical compositions can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg,

about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered three times per day.

In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of one day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of two days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of three days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of four days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of five days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of six days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of seven days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of eight days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of nine days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of ten days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 11 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 12 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 13 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 14 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 15 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 16 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 17 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 18 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 19 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 20 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 21 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 22 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 23 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 24 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 25 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 26 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 27 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 28 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 29 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 30 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 31 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 32 days. In some embodiments, the compound of Formula (I), or an isotopic

variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 33 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 34 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 35 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 36 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 37 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 38 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 39 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 40 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 41 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 42 days or more.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an

isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 14 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg twice daily for a period of up to

at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 14 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 220 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 28 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable

salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an

isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 28 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 255 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 42 days. In

certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 42 days.

In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg

twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 42 days.

In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, or about 800 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered at least once per day.

In certain embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day.

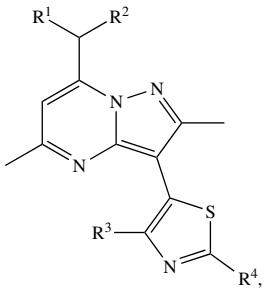
In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 6 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than

about 5 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 3 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 1 hour before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

In another aspect is provided a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I): and a pharmaceutically acceptable excipientcomprising with a compound as described herein, including embodiments, or the structural Formulae (I) and a pharmaceutically acceptable excipient:



or a pharmaceutically acceptable salt thereof. $R^1$, $R^2$, $R^3$, and $R^4$ are as described herein, including embodiments.

In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the pharmaceutical composition is administered orally.

In certain embodiments, the pharmaceutical composition is formulated as a capsule or tablet. In certain embodiments, the capsule or tablet comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 50 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 200 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the

subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

In certain embodiments, the pharmaceutical composition is administered in the fed state. In certain embodiments, the pharmaceutical composition is administered in the fasted state. In certain embodiments, the pharmaceutical composition is administered at least once per day.

In certain embodiments, the pharmaceutical composition is administered at bedtime. In certain embodiments, the pharmaceutical composition is administered less than about 6 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 5 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 3 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 1 hour before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep.

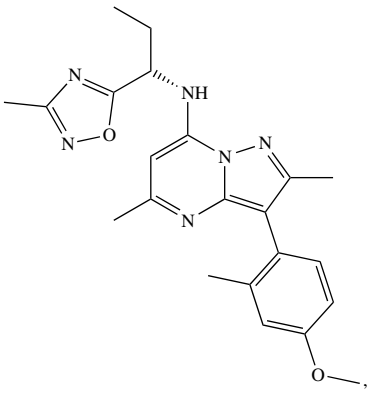
In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

In certain embodiments, the the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In certain embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In certain embodiments, the mineralocorticoid is fludrocortisone. In certain embodiments, the additional chemotherapeutic agent is another $CRF_1$ antagonist. In certain embodiments, the $CRF_1$ antagonist is:



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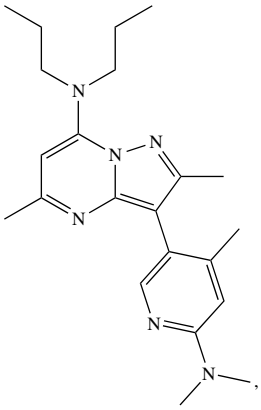

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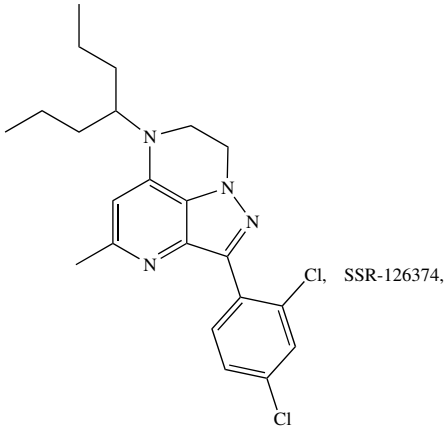

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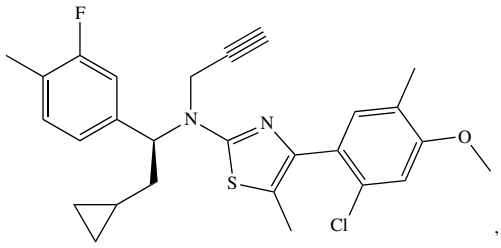

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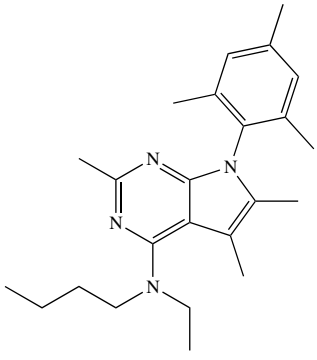

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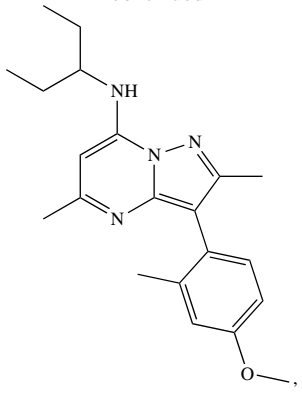
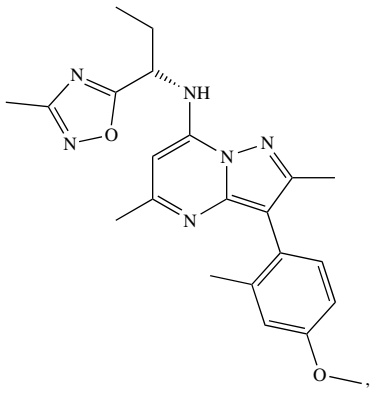


or a pharmaceutically acceptable salt thereof. In certain embodiments, the $CRF_1$ antagonist is



or a pharmaceutically acceptable salt thereof.

In certain embodiments of the methods disclosed herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In certain embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In certain embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the radiation therapy is prior to administration of the $CRF_1$ antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. In some embodiments, a tablet comprises a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil, or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. In some embodiments, a capsule comprises a solid carrier such as gelatin.

In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer's injection, or Lactated Ringer's injection. In some embodiments, preservatives, stabilisers, buffers, antioxidants, and/or other additives are included as required.

In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (see, *Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology,* 2nd Edition, Rathbone et al., Eds., Marcel Dekker, Inc.: New York, NY, 2008).

The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxy-

ethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

Coloring and flavoring agents can be used in all of the above dosage forms.

The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (see, *Remington: The Science and Practice of Pharmacy*, supra).

The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, N-methyl-2-pyrrolidone, N,N-dimethylacetamide, and dimethyl sulfoxide.

Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing

agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungi static concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and metliacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

V. Examples

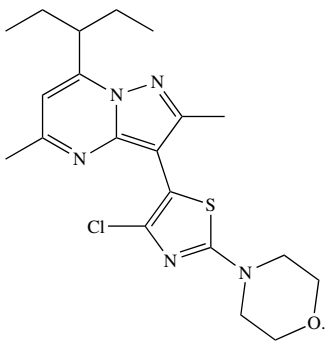
While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors

Testicular adrenal rest tumors (TART) is a common complication in congenital adrenal hyperplasia (CAH) that is caused by adrenocorticotropin hormone (ACTH)-driven overstimulation of aberrant adrenal cells within the testes and results in impaired spermatogenesis and infertility. TARTS can be found anywhere on the testes, though a typical (very common) location is within the mediastinum. This is a particularly problematic location. Because of the central location of TARTs being in the mediastinum, compression of the nearby seminiferous tubules is common and can lead to obstructive azoospermia, irreversible damage to surrounding tissue, and permanent infertility in males.

Current treatment for TART consists of chronic high-dose glucocorticoids, a problematic therapy with significant side effects and a narrow therapeutic window. Given the serious nature of TART and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with TART. Compound 1, a high-affinity and selective small-molecule antagonist of the corticotropin-releasing factor type-1 ($CRF_1$) receptor, may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH (FIG. **12**A-**12**B). Compound 1 has been shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. These promising results provide a rationale for investigating the use of Compound 1 in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.

The structure of Compound 1 is.




Building upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2 proof-of-concept study of Compound 1 in subjects with CAH, this Phase 2 will study Compound 1 specifically in male CAH subjects with TART for the first time. A sample size of approximately 12 subjects was selected to provide sufficient data for an initial evaluation of efficacy and safety in subjects with TART while maintaining feasible subject recruitment goals for this rare condition. Given the rarity of

the disease and thus the small sample size that can be recruited, this study will be open label, and all enrolled subjects will receive active study drug. Subjects will serve as their own controls in that their outcome measures after 12 weeks of study drug dosing will be compared to their baseline measures.

The schedule of study visits (every 2 weeks through Week 4, then every 4 weeks for the remainder of the study) provides an appropriate balance between minimizing subject burden and closely monitoring subject safety and response to therapy. The 4-week post-treatment washout period will allow for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

The specification of study drug dosing at 10 pm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers. The plasma $C_{max}$ (maximum concentration) for Compound 1 in the Phase 1 studies occurred approximately 5 hours after dosing. Therefore, Compound 1 will be dosed daily at 10 pm in this study in order to achieve peak plasma study drug concentration at the time of day when most adrenal androgens are produced. Subjects will consume a standardized snack before taking study drug because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety. (FIGS. **1**A-**1**B).

| Objectives | Endpoints |
|---|---|
| Primary | |
| To assess the efficacy of Compound 1 in subjects with TART | Reduction in the size/volume of TART on testicular ultrasound from screening to Week 12 |
| Secondary | |
| To evaluate the safety of Compound 1 in subjects with TART | Adverse events (AEs), serious adverse events (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs)<br>Physical examination findings<br>Vital signs<br>Changes in electrocardiogram (ECG)<br>Changes in clinical laboratory values |
| To assess the pharmacodynamic (PD) biomarker effects of Compound 1 | Changes in plasma concentrations of key PD biomarkers, including ACTH, 17-OHP, testosterone, androstenedione, luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, and aldosterone from baseline to Week 12 |
| To assess changes on semen analysis | Changes in sperm count, morphology, and motility from baseline to Week 12 |
| To assess changes in metabolism | Changes in metabolic parameters, including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12<br>Changes in body weight, body mass index (BMI), waist circumference, and blood pressure |
| To evaluate changes in quality of life (QoL) and mood | Changes in QoL measured using the Short Form 36 (SF-36)<br>Changes in mood measured using the Hospital Anxiety and Depression Scale (HADS) |

Study Population

Approximately 12 male subjects with TART will be enrolled at approximately 6 investigative sites in the United States, United Kingdom, and possibly other countries. Up to 12 additional subjects may be added to further evaluate specific safety, PD, or efficacy findings.

Eligibility Criteria

Inclusion Criteria

- Adult male subjects aged 18 to 30, inclusive
- Documented historical diagnosis of CAH based on documented genetic mutation or historical documentation of elevated 17-OHP
- Diagnosis of TART via testicular ultrasound and/or magnetic resonance imaging (MRI) at screening with ≥1 lesion(s) measuring ≥2 cm in diameter
- On a stable regimen of GC replacement for ≥30 days before baseline
- Agree to follow contraception guidelines and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug
- Subject is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Exclusion Criteria

- Any clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
  - A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
  - Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 $m^2$
  - Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
  - Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
- Any clinically significant psychiatric disorders, including any current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months
- HADS score >12 for either depression or anxiety
- At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at screening and baseline (eg, C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)
- Clinically significant and abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:
  - Clinically meaningful abnormal ECG results, in the opinion of the Investigator
  - Fridericia-corrected QT interval (QTcF) >450 msec
  - Alanine aminotransferase (ALT) >2× upper limit of normal (ULN)
  - Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- A history that includes bilateral adrenalectomy or hypopituitarism
- Use of any other investigational drug within 30 days or 5 half-lives, whichever is longer, before initial screening
- Require use of prohibited concomitant medications, including strong inhibitors and/or inducers of CYP3A4

(with the exception of glucocorticoids, hydrocortisone, and dexamethasone) within 30 days or 5 half-lives (whichever is longer) of first dose of study drug. Medications that are sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.

Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

Study Duration

The expected duration of study participation for each subject is up to approximately 20 weeks. This includes a screening period of 54 weeks, a treatment period of 12 weeks, and a safety follow-up period of 4 weeks.

Study Design

This is a Phase 2, open-label efficacy and safety study of Compound 1 for the treatment of TART. All subjects will receive a daily oral dose of Compound 1 for 12 weeks. In-clinic study visits will occur for screening and at Day 1 (baseline) and Weeks 2, 4, 8, 12 (end of treatment), and 16 (follow-up).

Dose, Route, Regimen

All subjects will receive a daily oral dose of Compound 1 for 12 weeks. Subjects will receive 600 mg/day during the first 2 weeks and 1000 mg/day during the remaining 10 weeks of the treatment period. Study drug will be taken daily at 10 pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

On mornings of study visits with 8 am blood draws for laboratory assessments, subjects should take their morning glucocorticoid replacement after the blood draws. For all other days during the study, subjects may take their morning glucocorticoid replacement at their usual time (generally between 6 am and 8 am).

If a subject experiences a Grade 3 or higher TEAE considered at least possibly related to study drug, the Investigator may reduce the subject's daily dose of Compound 1 down in increments of 200 mg. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria.

Investigational Drug

Compound 1 is a small-molecule $CRF_1$ receptor antagonist and will be supplied as 200-mg, size 1, white, hard gelatin capsules.

Example 2.

Since elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1, a small-molecule antagonist of the $CRF_1$ receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. **12**A-**12**B). The safety profile of Compound 1 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH is currently ongoing.

Nonclinical Toxicology of Compound 1

The nonclinical safety profile of Compound 1 has been evaluated in repeat-dose range-finding and definitive toxicology studies of up to 91 days in duration in rats and dogs using the clinically relevant route (oral) and schedule of administration (once daily). In rats and beagle dogs administered oral Compound 1 once daily for 91 consecutive days at doses up to 2000 mg/kg/day, toxicologic findings were all mild and limited to the male reproductive tract, and all Compound 1-related findings were reversible following a 6-week treatment-free recovery period.

Additionally, a fertility toxicology study was conducted in rats. In this study, male rats were administered oral Compound 1 once daily at 0, 5, 20, or 1000 mg/kg for 85 to 87 days (70 days before mating, during mating, and ≤4 days between mating and necropsy). Male reproductive performance (mean day of mating, mating and fertility indices, and conception rates) was unaffected by Compound 1 treatment. Untreated females mated with the Compound 1-treated males had no ovarian and uterine effects.

In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay have also been conducted.

Clinical Experience with Compound 1

To date, a total of 53 subjects, all healthy adults aged 21 to 65 years, have been treated with at least 1 dose of Compound 1 in 2 Phase 1 studies. The first-in-human study of Compound 1 (Study I3C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study I3C-FW-BLAB) evaluated repeat doses of 50 mg, 100 mg, or 200 mg Compound 1 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs). Compound 1 has been well tolerated in healthy human subjects, with no SAEs, AEs leading to discontinuation, or dose-limiting toxicities (DLTs). A maximum tolerated dose has not been reached in humans.

An ongoing Phase 2 open-label study (Study Compound 2) is currently evaluating the safety and efficacy of Compound 1 dosed once daily for 6 weeks in adults with classic CAH. In the initial Cohort A of this study, all subjects are dosed starting at 200 mg/day for 14 days, escalating for each subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLTs at the previous dose level. (FIGS. **2**-**3**).

Known Potential Risks

Because the reversible testicular effects (degeneration/atrophy) observed in rats and dogs treated with high-dose Compound 1 (2,000 mg/kg/day) are likely associated with on-target (mechanism-driven) effects, these effects are likely to be relevant to human risk. However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical laboratory markers of testicular function (LH and FSH) when Compound 1 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Clinical laboratory measures of testicular function (LH, FSH, inhibin B, and SHBG) will be assessed throughout this study to monitor the risk of tes-

ticular injury. Testicular ultrasounds and semen analysis will also be performed at screening/baseline and the end of the treatment period.

Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the Phase 1 clinical studies. Clinical laboratory measures of liver chemistry will be assessed throughout this study, and strict individual treatment stopping criteria for liver chemistry findings are in place.

Compound 1-induced effects on the thyroid gland were noted in dogs after 91 days of high-dose (2,000 mg/kg/day) treatment but not in any other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) were not evaluated in the Phase 1 studies but will be monitored throughout this study.

Known Potential Benefits

Early clinical studies suggests that Compound 1 is effective as a $CRF_1$ receptor antagonist, a mechanism of action that supports the clinical investigation of Compound 1 for treatment of TART. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule $CRF_1$ receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. **12**A-**12**B).

Assessment of Potential Risks and Benefits

The mild and reversible toxicologic effects of Compound 1 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a $CRF_1$ receptor antagonist, Compound 1 is intended to reduce abnormally elevated ACTH levels, which in TART drives overstimulation of aberrant adrenal cells within the testes. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. In TART, where baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

Given the serious nature of TART and the limitations (and risks) of chronic steroid therapy, new treatment modalities are needed for patients with TART. Given the acceptable safety and tolerability profile of Compound 1 in healthy volunteers from the Phase 1 program, the low probability of demonstrating meaningful PD marker changes in healthy subjects, and the lack of any clear benefit to exposing more healthy subjects to study drug, the Sponsor believes the benefit-to-risk profile favors the entry of Compound 1 into Phase 2 in subjects with TART.

Example 3. Congenital Andrenal Hyperplasia (CAH)

CAH results from a genetic defect in the 21-hydroxylase enzyme. CAH patients are thus unable to produce cortisol. Without cortisol to provide negative feedback, patients over-produce ACTH. High ACTH promotes the overproduction of potent androgens (male sex hormones). Without wishing to be bound by theory, Compound 1 blocks $CRF_1$ receptor to prevent ACTH release by the pituitary and associated drive on the hypothalamic-pituitary-adrenal axis. Replacement of cortisol to physiological levels will correct cortisol deficiency, however, will not lower ACTH, resulting in hyperplasia of adrenal gland and associated overproduction of adrenal androgens.

As shown in FIGS. **4** and **5**A-**5**B, the attenuation of ACTH demonstrates target engagement and functional $CRF_1$ receptor antagonism. 80% of subjects demonstrated reduction in ACTH. 70% of subjects demonstrated >25% reduction in ACTH. 30% of subjects were in the normal range (*) after treatment with a $CRF_1$ receptor antagonist.

FIGS. **6** and **7**A-**7**B demonstrate "control" of disease based on standard guidelines, which would then allow steroid taper. 80% of subjects demonstrated reduction in 17-OHP. 50% of subjects demonstrated >25% reduction in ACTH. 50% of subjects were in the guideline range (*; 1200 ng/dL) after treatment with a $CRF_1$ receptor antagonist.

FIGS. **8** and **9**A-**9**B demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess androgen production and associated symptoms. 100% of subjects demonstrated reduction in androstenedione (at various doses). 60% of subjects demonstrated >25% reduction in androstenedione. 50% of subjects were within the normal reference range after treatment with a $CRF_1$ receptor antagonist.

FIGS. **10**A-**10**B show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a $CRF_1$ receptor antagonist.

FIGS. **11**A-**11**B demonstrate Compound 1 is a potent, selective, and functional $CRF_1$ receptor antagonist. In in vitro and ex vivo studies, Compound 1 was determined to be a potent and selective $CRF_1$ receptor antagonist with high affinity and selective for the $hCRF_1$ receptor. Compound 1 was found to have functional potency to inhibit adenylate cyclase activity ($CRF_1$ receptor-mediated downstream cascade), demonstrating in vitro efficacy as a $CRF_1$ receptor antagonist. Compound 1 was found to significantly inhibit CRF-induced locomotor behavior in response to i.e.v. administration of CRF (FIG. **11**B).

FIGS. **12**A-**12**B demonstrate single pill of $CRF_1$ receptor antagonist (i.e., as described in US 2017/0020877 A1) improves ACTH and 17-OHP in CAH patients.

FIG. **13** shows the subject level hormone changes (ACTH, 17-OHP, and androstenedione) by dose of a $CRF_1$ receptor antagonist.

Example 4. Assess Reduction in Excess ACTH and Adrenal Steroid Production

The objectives of the study are: to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable gluococorticoid regimen; to evaluate the safety and tolerability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

Eligibility Criteria

Inclusion Criteria:

- Adult males and females 18 years or older
- Diagnosis of classic CAH due to 21-hydroxylase deficiency
- Morning 17OHP ≥800 ng/dL, before taking any morning GC dose
- On a stable regimen of gluococorticoid replacement for ≥30 days before enrollment

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease within 30 days of screening
- Clinically significant psychiatric disorder
- History of bilateral adrenalectomy or hypopituitarism

Study Design

FIG. **14** depicts the proof of concept and escalating QD dosing at 10 PM for Cohort A and the single dose level and BID dosing at 10 AM and 10 pm for Cohort B.

Baseline Characteristics

Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 partcipants were enrolled and received at least 1 dose of

Compound 1. One participant withdrew early because of an occupation-related scheduling conflict. In Cohort B, 9 participants were enrolled and received at least one dose of Compound 1. One participant was withdrawn upon discovery of a major protocol violation at Baseline and did not have postbaseline efficacy/PK data. Thus, baseline characteristics are calculated for n=8 in Cohort B. One participant in Cohort B was taking both HC and prednisone.

TABLE 1

Baseline characteristics of each cohort

| Parameter | Cohort A (n = 10) | Cohort B (n = 8) |
|---|---|---|
| Demographics | | |
| Age (years), mean (range) | 39.3 (24-66) | 36.8 (19-66) |
| Sex | 5 M, 5 F | 1 M, 7 F |
| Bmi (kg/m$^2$), mean ± SD | 31.5 ± 12.0 | 31.1 ± 6.7 |
| Daily GC dose (mg HC equivalents), mean range | 28 (13-40) | 35 (20-50) |
| Types of GCs | 4 JC, 3 pred, 3 dex | 2 HC, 4 pred, 3 dex |
| 17OHP at screening[a] (ng/dl), mean ± SD | 5,985 ± 6,347 | 4,592 ± 4,624 |

Abbreviations:
17OHP: 17-hydroxyprogesterone;
BMI: body mass index;
dex: dexamethasone;
F: female;
GC: glucocorticoid;
HC: hydrocortisone;
M: male;
pred: prednisone;
SD: standard deviation.
[a]17OHP reference ranges: 27-199 ng/dL males, 15-290 ng/dL females.

Safety

Across both cohorts, Compound 1 was generally well tolerated. The most common type of adverse event (AE) was gastrointestinal disorders There were no serious AEs and no AEs leading to withdrawal.

Pharmacokinetics

Over a wide range of doses (200 to 1000 mg QD), Compound 1exhibited a predictable, dose-dependent PK profile.

Efficacy

FIG. **15**A-**15**D show the changes in levels of Androstenedione (A4) across both cohorts. Levels of A4 improved at ≥1 dose level for 10 out of 10 participants in Cohort A and 6 out of 8 participants in Cohort B. Excess A4 is associated with clinical sequelae in CAH. Attenuation of A4 demonstrates control of adrenal androgen.

FIG. **16**A-**16**D show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at 1 dose level for 8 out of 10 participants in Cohort A and 6 out of 7 participants in Cohort B. 17OHP is a critical hormone in CAH diagnosis and management. Attenuation of 17OHP demonstrates control of adrenal steroid production.

FIG. **17**A-**17**D show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at 1 dose level for 8 out of 10 participants in Cohort A and 5 out of 7 participants in Cohort B. Attenuation of ACTH demonstrates target engagement and fucntional $CRF_1$ receptor antagonism.

TABLE 2

Percentage change from baseline in ACTH, 17OHP and A4.

| | Cohort A | | | Cohort B |
|---|---|---|---|---|
| | 200 mg QD (Week 2) | 600 mg QD (Week 4) | 1000 mg QD (Week 6) | 200 mg BID (Weed 2) |
| ACTH | −25.7 (±51.6) | −60.1 (±37.5) | −32.7 (±47.0) | −36.5 (±58.0) |
| 17OHP | +22.2 (±172.3) | −23.7 (±64.2) | −13.8 (±74.7) | −47.8 (±63.3) |
| A4 | −12.1 (±47.4) | −33.2 (±36.5) | −28.6 (±44.6) | −16.0 (±81.4) |

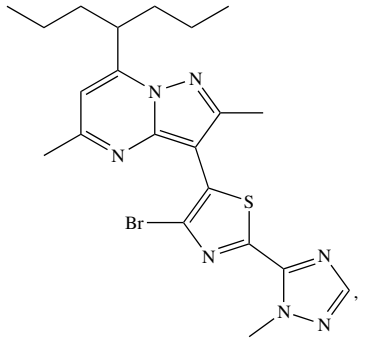
## CONCLUSIONS

Compound 1, a potent and selective $CRF_1$ receptor antagonist, offers a novel nonsteroidal oral treatment approach for CAH. Compound 1 was well tolerated and efficacious in reducing excess ACTH, 17OHP, and androstenedione in patients with classic CAH. Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

**1**. A method of treating an endocrine disorder associated with corticotropin-releasing factor type-1 ($CRF_1$) activity, comprising administering to a subject in need thereof a small molecule $CRF_1$ antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule $CRF_1$ antagonist is:



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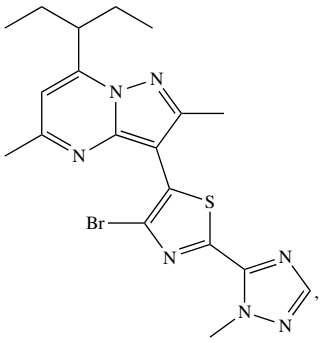

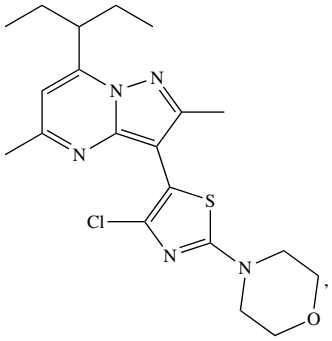

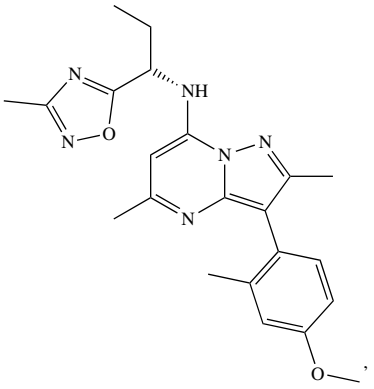

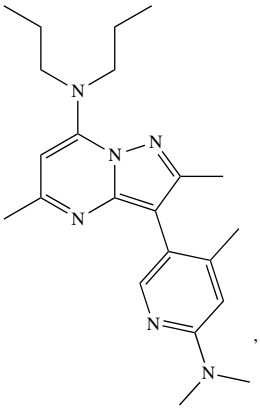

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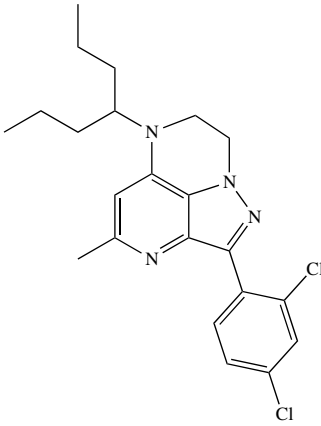

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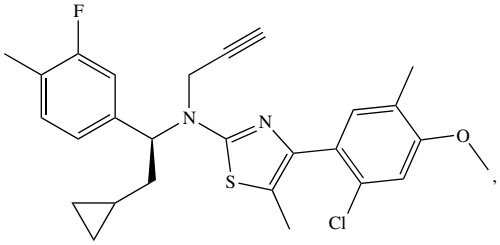

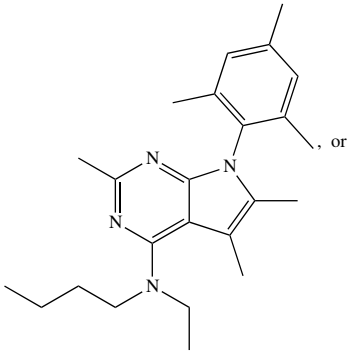

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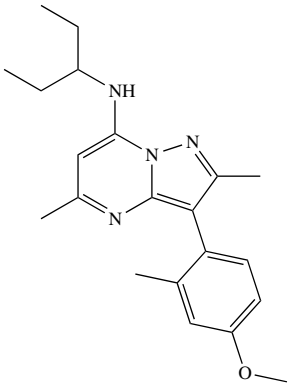


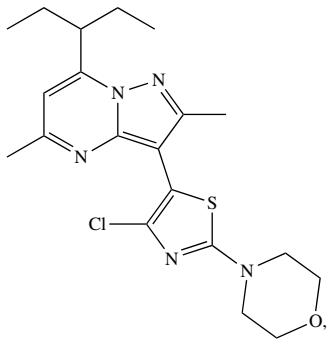
or a pharmaceutically acceptable salt thereof,

wherein the small molecule $CRF_1$ antagonist is administered to the subject twice per day, and

wherein the subject is in the fed state,

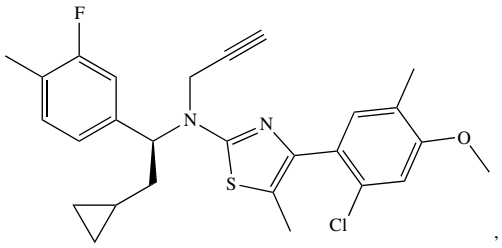
wherein the endocrine disorder associated with $CRF_1$ activity is a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART).

**2**. The method of claim **1**, wherein the small molecule $CRF_1$ antagonist is:



or a pharmaceutically acceptable salt thereof.

**3**. The method of claim **1**, wherein the small molecule $CRF_1$ antagonist is:



or a pharmaceutically acceptable salt thereof.

**4**. The method of claim **1**, wherein the subject has congenital adrenal hyperplasia (CAH).

**5**. The method of claim **1**, wherein the subject is receiving a glucocorticoid in conjunction with the administering of the small molecule $CRF_1$ antagonist.

**6**. The method of claim **5**, wherein the glucocorticoid comprises beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone, or a combination thereof.

**7**. The method of claim **6**, wherein the glucocorticoid is hydrocortisone.

**8**. The method of claim **1**, wherein the subject is an adolescent.

**9**. The method of claim **1**, wherein the subject is at least 18 years old.

**10**. The method of claim **1**, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.

**11**. The method of claim **10**, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 50 mg.

**12**. The method of claim **10**, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 100 mg.

**13**. The method of claim **10**, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 200 mg.

**14**. The method of claim **1**, wherein the small molecule $CRF_1$ antagonist is administered at a dose of about 400 mg.

**15**. The method of claim **1**, wherein the small molecule $CRF_1$ antagonist is administered orally.

**16**. The method of claim **1**, wherein the small molecule $CRF_1$ antagonist is formulated as a capsule or tablet.

**17**. The method of claim **1**, wherein the small molecule $CRF_1$ antagonist is administered less than about 6 hours before sleep.

**18**. The method of claim **1**, wherein the small molecule $CRF_1$ antagonist is administered less than about 3 hours before sleep.

**19**. The method of claim **1**, wherein the small molecule $CRF_1$ antagonist is administered in the evening.

* * * * *

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