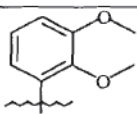
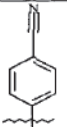
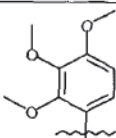
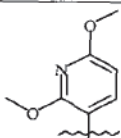
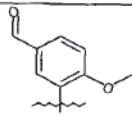
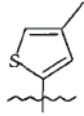
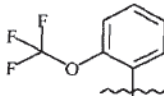
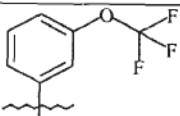
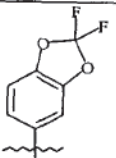
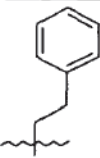
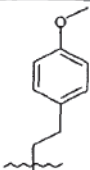
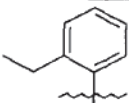
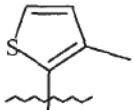
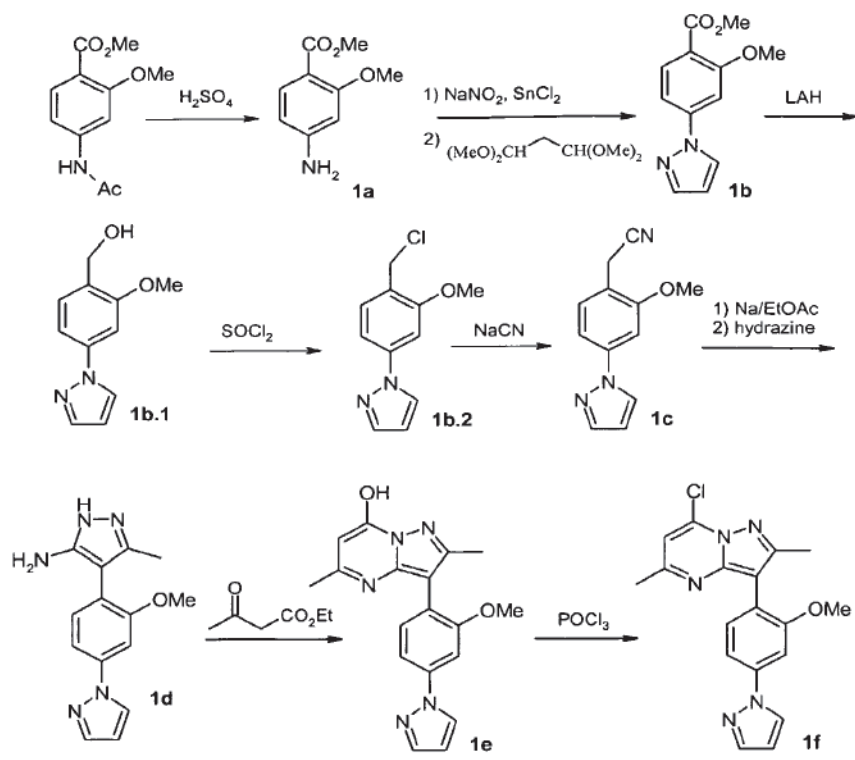


Cmpd	R ₂	MW	MS	t _R	HPLC Method
1-60		455.52	455	6.170	2
1-61		420.47	420	1.410	4
1-62		485.54	486	7.540	2
1-63		456.50	456	8.120	2
1-64		453.50	454.3	5.710	2
1-65		415.52	415	6.770	2
1-66		399.46	399	6.430	2
1-67		479.46	479	6.740	2
1-68		479.46	479	7.260	2
1-69		475.45	475	6.970	2
1-70		423.52	423	6.370	2

Cmpd	R ₂	MW	MS	t _R	HPLC Method
1-71		453.54	453	6.280	2
1-72		423.52	423	8.420	2
1-73		415.52	415	8.080	2

EXAMPLE 1A**ALTERNATE SYNTHESIS OF INTERMEDIATE 1F****Step 1A-A:**

- 5 To a 3-neck flask equipped with a mechanical stirrer was charged 250 g (1.12 mol) of 2-methoxy-4-acetylaminobenzoic acid methyl ester followed by 1L of methanol. Agitation was started and 94 mL (3.36 mmol, 3 eq.) of concentrated sulfuric acid was slowly added creating a slight reflux. The mixture was stirred for 24 hr. The mixture was concentrated *in vacuo* affording
- 10 a thick slurry. The slurry was filtered using a Buchner funnel and washed with 300 mL of cold methanol. The filter cake was collected and dried *in vacuo* at 45 °C for 24 hr affording 302 g of **1a** as a hemi-sulfate salt in a 96% yield.

Step 1A-B:

- 15 In a 2L three-neck Morton flask equipped with a mechanical stirrer and thermocouple was charged 200 g (716 mmol) of methyl 4-amino-2-methoxybenzoate

- 1a.** The solid was slurried with 700 mL of 6N hydrochloric acid and chilled in an ice-bath. To the mixture was charged dropwise 54.3 g (788 mmol, 1.1 eq.) of sodium nitrite in 100 mL of water maintaining a temperature of <15 °C during the addition. The mixture was stirred an additional 1.5 hr affording a light yellow, homogeneous solution.
- 5 To the mixture was carefully added 272 g (1432 mmol, 2 eq.) of anhydrous stannous chloride. The temperature during the addition was kept <10 °C. The mixture was stirred at 0 °C for 1 hr, and then stored at 5 °C for 16 hr. The precipitate was collected by filtration through a Buchner funnel and the filter cake air dried for 2 hr. The filter cake was transferred to a 2 L round bottom flask equipped with a magnetic stir bar and
- 10 diluted with 600 mL of ethanol. To the slurry was charged 142 mL (859 mmol, 1.2 eq.) of malonaldehyde bis(dimethyl acetal) and the mixture refluxed for 6 hr. After evaporation of ethanol, the residue was diluted with ethyl acetate and neutralized with sodium hydroxide. The organic phase was separated, dried and concentrated in vacuo. The crude product was passed through a silica gel plug eluting with 25% ethyl
- 15 acetate in hexane affording 96 g of Cmpd **1b** in a 58% yield as a mixture of the methyl and ethyl esters.

Step 1A-C:

- To a 1L round bottom flask containing 500 mL dry THF was added LAH (14.5 g, 380 mmol, 0.95 eq), and the mixture was cooled to 0 °C. To this mixture was
- 20 added dropwise a solution of **1b** (96 g, 400 mmol, 1.0 eq) in 300 mL THF. The temperature was maintained below 15 °C during the addition. After the addition was complete, the mixture was stirred for 1 hr, then the reaction mix was carefully quenched with water (14.5 mL), 10% aq. sodium hydroxide (14.5 mL), and water (43.5 mL). The resulting mixture was filtered through a pad of Celite® and concentrated to
- 25 provide **1b.1** as a slightly yellow oil (63.9 g, 75.7%), which was used without further purification.

Step 1A-D:

- Thionyl chloride (95 mL, 1.30 mol, 3.1 eq) was added dropwise over 1 hr to a solution of **1b.1** (85.0 g, 0.42 mol) in 400 mL DCM, keeping the rate of addition
- 30 such that a gentle reflux was maintained. A precipitate formed, which re-dissolved upon completion of the addition. The resulting dark solution was refluxed for 4 hr. The cooled reaction mixture was poured onto 500 g of ice, and the resulting mixture was extracted with 2 x 700 mL of DCM. The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and

concentrated to provide **1b.2** (76.5 g) as a brown solid, which was used without further purification.

Step 1A-E:

A solution of **1b.2** (76 g, 340 mmol, 1.0 eq.) in DMF (100 mL) was added dropwise over 20 min. to a mixture of sodium cyanide (24.5 g, 500 mmol, 1.5 eq) and DMF (300 mL) heated to 100 °C. The mixture was heated at 100 °C for 4 hr, then the cooled mixture was filtered through Celite®. The filtrate was concentrated, then the residue was taken up in 300 mL DCM and washed with saturated aqueous sodium bicarbonate solution (200 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to provide a dark brown solid residue. This residue was slurried in ethanol (100 mL), then the solid was collected by filtration and washed with cold ethanol and ether, providing **1c** (48.0 g) as an off-white solid. The mother liquid was concentrated and purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide an additional 15.4 g of **1c** as a white solid. Combined yield 63.4 g.

Step 1A-F:

To a solution of **1c** (63.4 g, 0.30 mol, 1 eq) in ethyl acetate (800 mL) was added metallic sodium (10.3 g, 0.45 mmol, 1.5 eq) portionwise, and the mixture was refluxed for 16 hr. The cooled suspension was poured onto 500 g ice, acidified to pH 5, then extracted with 2 x 300 mL ethyl acetate. The organic phase was dried over sodium sulfate, filtered, and concentrated to a crude yellow oil (86.5 g).

The crude yellow oil (86.5 g) was dissolved in ethanol (480 mL) and water (80 mL), then hydrazine monohydrobromide (100 g, 0.88 mol, 3 eq) was added and the mixture was heated at 85 °C for 16 hr. The solvents were evaporated, brine (200 mL) was added, and the mixture was extracted with 2 x 300 mL ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to provide **1d** (68 g) as a crude brown foam, which was used without further purification.

Step 1A-G:

A mixture of **1d** (68 g, 250 mmol, 1.0 eq), ethyl acetoacetate (100 mL), acetic acid (150 mL), and ethanol (150 mL) was refluxed for 24 hr. The cooled mixture was concentrated to provide a solid residue, which was then deposited onto a fritted glass filter and washed with ether, providing **1e** (52.0 g, 51.2%) as an off-white solid.

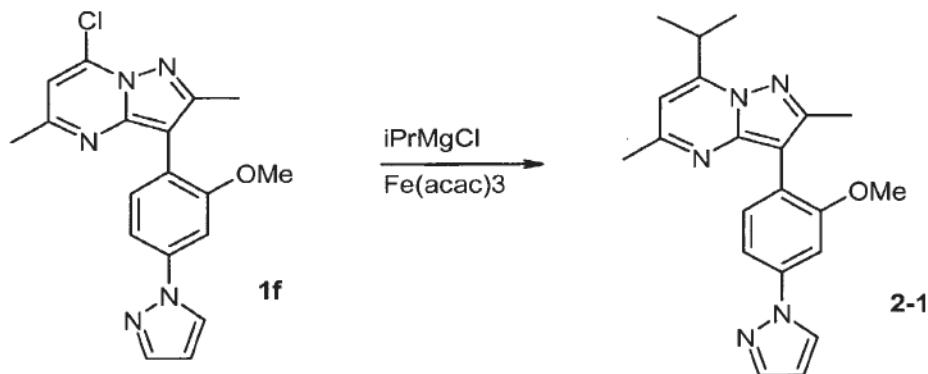
The mother liquor was concentrated, then chromatographed on silica gel using 10% methanol in DCM as eluent. The solid product thus obtained was washed with ether to provide an additional 17.0 g of **1e** as an off-white solid (combined yield 69 g).

Step 1A-H:

- 5 To a suspension of **1e** (41.2 g, 123 mmol) in acetonitrile (200 mL) was added POCl_3 (45.0 mL, 493 mmol,) and this mixture was refluxed for 16 hr. The cooled reaction mixture was poured onto ice-water, and the resulting mixture was extracted with chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography,
10 eluting with 3:1 hexanes/ethyl acetate, to yield **1f** (29.0 g) as a tan solid.

EXAMPLE 2

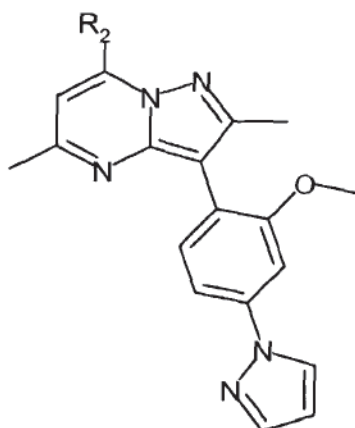
7-ISOPROPYL-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



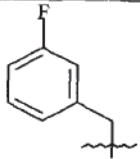
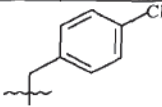
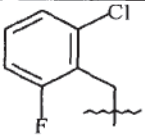
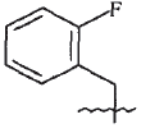
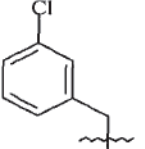
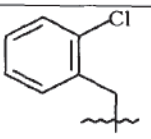
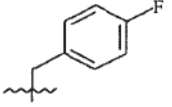
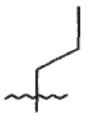
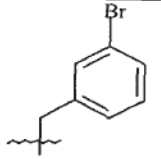
15 Step 2A:

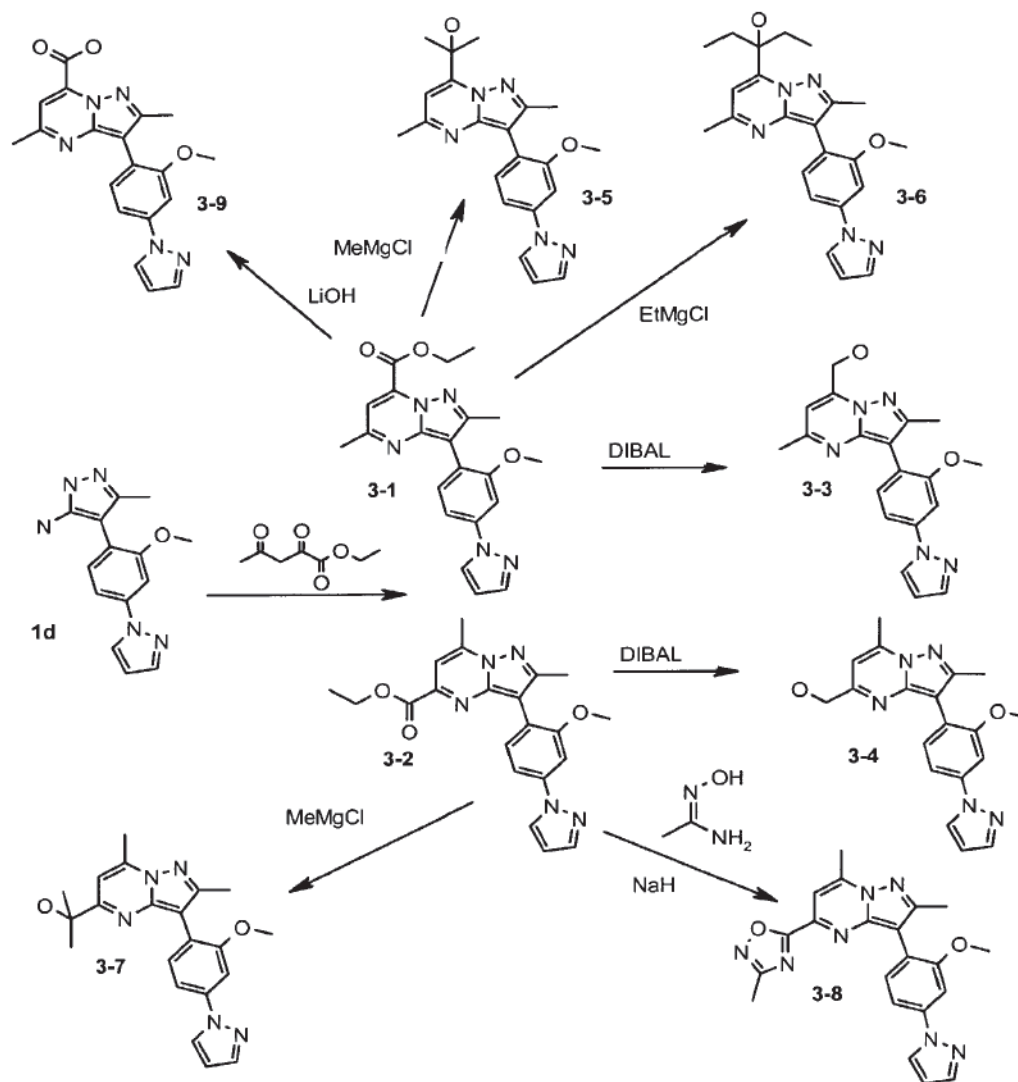
- To a solution of Cmpd **1f** (1.41 g, 4.0 mmol) and Fe(acac)_3 (424 mg, 1.2 mmol) in THF/NMP (v/v = 8:1) was added iPrMgCl (2.0 M in THF, 4.0 mL) slowly at room temperature. The reaction mixture was stirred for 1.5 hr before quenched with 1N HCl (aq.). After extraction with EtOAc, the crude product was purified by column
20 chromatography (25% EtOAc/Hexane) to yield Cmpd **2-1** (628 mg.)

Depending on the alkyl functionality in the alkyl magnesium halide, the compounds listed in the following table were synthesized:



Cmpd	R ₂	MW	MS	t _R	HPLC Method
2-1		361.447	361	1.286	4
2-2		375.474	375	1.499	4
2-3		333.393	333	1.542	4
2-4		375.474	375	1.278	4
2-5		389.5	390.2	8.490	2
2-6		347.42	348	6.514	2
2-7		415.417	415	7.880	2
2-8		409.491	409	6.280	2

Cmpd	R ₂	MW	MS	t _R	HPLC Method
2-9		427.481	428	8.240	2
2-10		443.936	444	8.790	2
2-11		461.926	462	8.740	2
2-12		427.481	428	8.240	2
2-13		443.936	444	8.750	2
2-14		443.936	444	8.660	2
2-15		427.481	428	8.240	2
2-16		361.447	361	2.700	1
2-17		488.387	488	8.920	2

EXAMPLE 3**3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE-7-CARBOXYLIC ACID ETHYL ESTER****5 Step 3A:**

To 20 mL EtOH were added Cmpd **1d** (1.0 g, Example 1, Step 1C) and ethyl-2,4-dioxovalerate (0.82 g) followed by 0.5 mL acetic acid. The reaction mixture was heated at 80 °C for 12 hr. Concentration and purification by silica gel column

chromatography yielded Cmpd **3-1** (0.66 g, 46.1% yield) and the inverted addition Cmpd **3-2** (0.47 g, 32.2% yield.)

Step 3B:

To Cmpd **3-1** (30 mg) dissolved in THF (1.5 mL) was added DIBAL (150
5 μ L of 2 M DIBAL in hexane.) The reaction mixture was stirred at room temperature for 2 hr and quenched with water (0.4 mL.) After purification via LC-MS, Cmpd **3-3** (3.3 mg) obtained. Following the same procedure, the reduction of Cmpd **3-2** afforded Cmpd **3-4** (2.6 mg) after purification.

Step 3C:

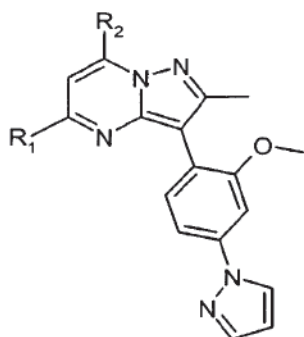
To 1.5 mL THF was added Cmpd **3-1** (30 mg) followed by CH_3MgBr
10 (150 μ L of 2 M CH_3MgBr in THF.) The reaction mixture was stirred at room temperature for 2 hr and quenched with water. The resulting material was purified by LC-MS to yield Cmpd **3-5** (3.8 mg.) Following this procedure with Cmpd **3-1** and $\text{CH}_3\text{CH}_2\text{MgBr}$ yielded Cmpd **3-6** (4.1 mg.) after purification. Following the same
15 reaction procedure employing Cmpd **3-2** as the starting reagent and CH_3MgBr as nucleophile afforded Cmpd **3-7** (4.0 mg) after purification.

Step 3D:

To THF (1.5 mL) was added acetamidoxime (20 mg) and NaH (10 mg)
with stirring at room temperature for 30 min. Cmpd **3-2** (40 mg) was added, and the
20 mixture was heated at 90 °C for 2 hr in a sealed tube. After purification via LC-MS, Cmpd **3-8** obtained (5.5 mg.)

Step 3E:

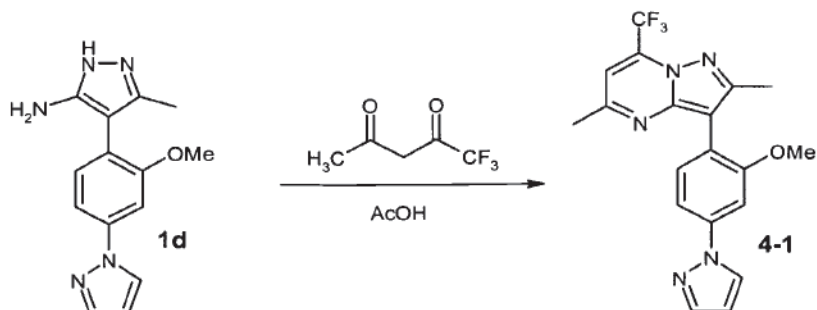
To Cmpd **3-1** (200 mg) in dioxane:water (9:1) was added LiOH (30 mg.)
The reaction proceeded with stirring for 6 hr at room temperature followed by
25 quenching to pH 4 (HCl, 4 N) and extraction between H_2O (20 mL) and EtOAc (20 mL.) The organic phase was dried over Na_2SO_4 and concentrated. The resulting concentrate was purified by silica gel column chromatography (50:50 EtOAc/hexane) to yield Cmpd **3-9** (180 mg.) Compounds presented in Example 3 are tabulated in the following table:



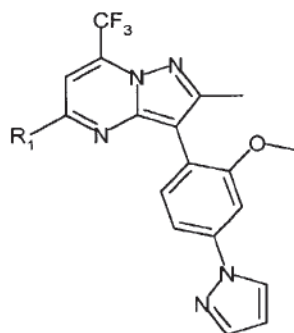
Cmpd	R ₁	R ₂	MW	MS	t _R	HPLC Method
3-1			391.429	392	2.681	1
3-2			391.429	392	6.850	2
3-3			349.392	350	5.060	2
3-4			349.392	350	5.030	2
3-5			377.446	378	6.880	2
3-6			405.499	406	7.980	2
3-7			377.446	378	1.264	4
3-8			401.428	402	6.990	2
3-9			363.375	364	5.740	2

EXAMPLE 4

3-(2-Methoxy-4-pyrazol-1-yl-phenyl)-2,5-dimethyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

**5 Step 4A:**

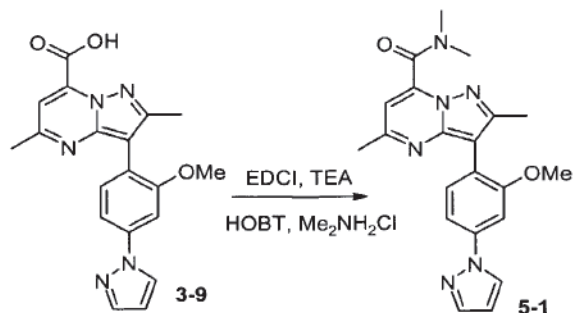
A mixture of Cmpd **1d** (40 mg, Example 1, Step 1C) and 1,1,1-trifluoropentane-2,4-dione (excess) was heated in AcOH at 150 °C for 15 min with microwave to afford after purification via LC-MS Cmpd **4-1** (29 mg.) Depending on the trifluorodione, the compounds in the following table were synthesized:



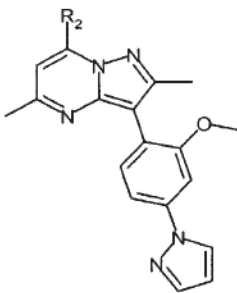
10

Cmpd	R ₁	MW	MS	t _R *
4-1		387.363	387	6.215
4-2		415.417	415	6.928

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 5**3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE-7-CARBOXYLIC ACID DIMETHYLAMIDE****5 Step 5A:**

To a solution of Cmpd **3-9** (50 mg, 0.14 mmol, 1 eq) in DCM (1 mL) was added HOBT (57 mg, 0.42 mmol, 3 eq), TEA (0.12 mL, 0.84 mmol, 6 eq), dimethylamine hydrochloride (34 mg, 0.42 mmol, 3 eq) and EDCI (79 mg, 0.42 mmol, 3 eq). The mixture was stirred at room temperature for 16 hr, then the solvent was evaporated, and the crude reaction mixture was purified by preparative HPLC/MS, providing Cmpd **5-1** (10 mg) as a TFA salt. Depending on the amine employed in the amidation step above, the compounds in the following table were synthesized:

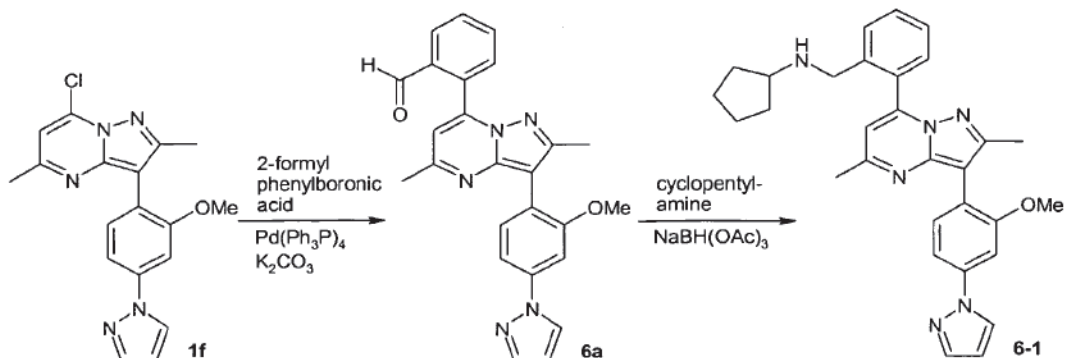


Cmpd	R ₂	MW	MS	t _R [*]
5-1	-C(O)N(CH ₃) ₂	390.44		5.17
5-2	-C(O)N(CH ₂ CH ₃) ₂	418.50	419.2	6.22
5-3	-C(O)N(CH ₃)CH ₂ CH ₃	404.47	405.2	5.66

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 6

CYCLOPENTYL-{2-[3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDIN-7-YL]-BENZYL}-AMINE

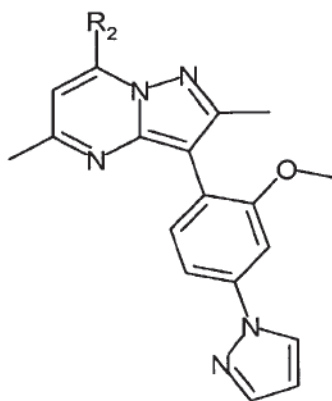
**5 Step 6A:**

To a solution of **1f** (500 mg, 1.4 mmol, 1 eq) in 1:1 dioxane/water (6 mL) was added 2-formylphenylboronic acid (255 mg, 1.7 mmol, 1.2 eq), followed by potassium carbonate (390 mg, 2.8 mmol, 2.0 eq) and tetrakis(triphenylphosphine)palladium(0) (82 mg, 0.07 mmol, 0.05 eq). The mixture was heated in a sealed tube at 100 °C for 3 hr, then the solvent was removed under vacuum. The residue was taken up in ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, concentrated, and the residue was purified by silica gel column chromatography using 1:1 hexanes/ethyl acetate as eluent, to afford **6a** (500 mg, 85%) as a yellow solid.

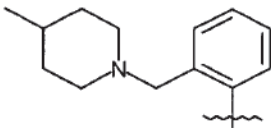
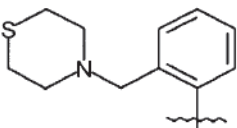
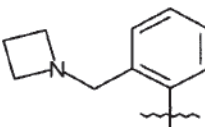
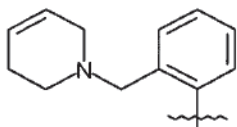
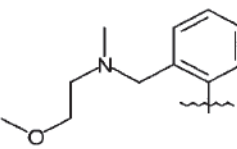
15 Step 6B:

Sodium triacetoxyborohydride (80 mg, 0.38 mmol, 2 eq) was added at RT to a solution of **6a** (80 mg, 0.19 mmol, 1 eq) and acetic acid (0.011 mL, 0.19 mmol, 1 eq) in dichloroethane (1 mL). The mixture was stirred at RT for 16 hr, then the mixture was concentrated, taken up in methanol, and purified directly by preparative HPLC/MS, providing **6-1** (36 mg, 38 % yield) as a TFA salt.

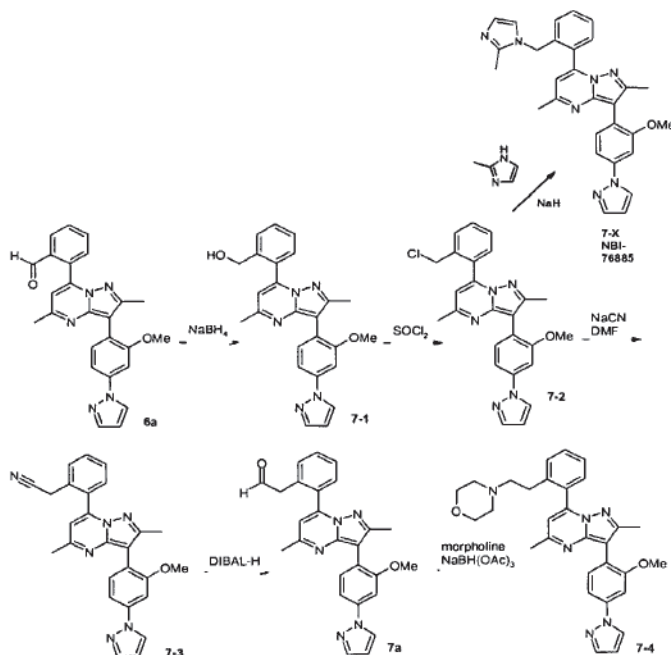
Depending on the amine employed in the reductive amination step above, the compounds of the following table were synthesized:



Cmpd	R ₂	MW	MS	t _R ⁺
6-1		492.62	493.4	5.69
6-2		506.65	507.4	5.95
6-3		478.60	479.1	5.49
6-4		466.59	467.1	5.33
6-5		452.559	452	4.40
6-6		478.597	478	4.70
6-7		492.624	492	4.85
6-8		506.651	506	4.74

Cmpd	R ₂	MW	MS	t _R
6-9		506.651	506	4.82
6-10		510.663	510	4.60
6-11		464.57	464	4.38
6-12		490.608	490	4.60
6-13		496.612	496	4.57

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 7**3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-[2-(2-MORPHOLIN-4-YL-ETHYL)-PHENYL]-PYRAZOLO[1,5-A]PYRIMIDINE****5 Step 7A:**

To a suspension of **6a** (345 mg, 0.82 mmol) in 1:1 THF/methanol (4 mL) at RT was added carefully sodium borohydride (62 mg, 1.6 mmol, 2 eq). The mixture was stirred for 30 min, then water was added and the mixture was extracted with DCM. The combined organic layers were washed with water and brine, then dried over sodium sulfate, filtered, and concentrated to provide **7-1** (450 mg, 90 %) as a solid, which was used without further purification.

Step 7B:

Thionyl chloride (0.17 mL, 2.3 mmol, 2.2 eq) was added to a solution of **7-1** (450 mg, 1.05 mmol, 1 eq) in DCM (5 mL) at RT. The mixture was stirred at RT for 30 min, then water was added and the mixture was extracted with DCM. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated to provide **7-2** (420 mg, 90 %) as a yellow solid.

Step 7-C

Sodium hydride (11 mg of 60 % dispersion in mineral oil, 0.28 mmol, 4 eq) was added to a solution of 2-Methylimidazole (17 mg, 0.21 mmol, 3 eq) in 2 ml DMF at rt. The mixture was stirred for 10 min, then a solution of 7-2 (30 mg, 0.07 mmol, 1 eq) in 0.2 ml DMF was added and the mixture was stirred at rt for 17 h. The mixture was diluted with methanol, then purified directly by preparative HPLC/MS, providing 7-X (6 mg) as a TFA salt.

Step 7D:

Sodium cyanide (3.3 mg, 0.067 mmol, 3 eq) was added to a solution of 7-2 (10 mg, 0.023 mmol, 1 eq) in DMSO (3 mL) at RT. The mixture was stirred at RT for 2 hr, then water was added and the mixture was extracted with DCM. The combined organic layers were washed with water and brine, then dried over sodium sulfate, filtered, and concentrated to provide crude 7-3 (8 mg, 80 % yield) as a solid.

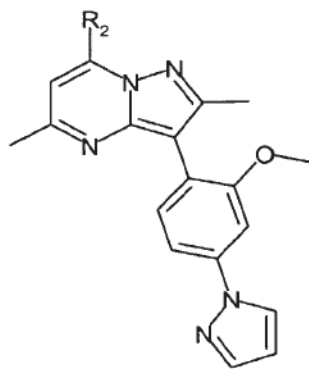
Step 7E:

DIBAL-H (0.23 mL of a 1.5 M solution in toluene, 0.35 mmol, 3 eq) was added to a solution of 7-3 (50 mg, 0.11 mmol) in DCM (1 mL) at -78 °C. The mixture was stirred at -78 °C for 20 min, then was allowed to warm to RT. Water was added and the mixture was stirred for 10 min, then the aqueous layer was extracted with two additional portions of DCM. The combined organic extracts were washed with water and brine, were dried over sodium sulfate, filtered through Celite®, and concentrated. The residue was purified by prep HPLC/MS to provide 7a (15 mg) as a TFA salt.

Step 7F:

Sodium triacetoxyborohydride (15 mg, 0.069 mmol, 2 eq) was added to a room temperature solution of 7a (15 mg, 0.034 mmol, 1 eq) and acetic acid (0.002 mL, 0.034 mmol, 1 eq) in DCM (1 mL). The mixture was stirred at RT for 16 hr, then the mixture was concentrated, taken up in methanol, and purified directly by preparative HPLC/MS, providing 7-4 (11 mg, 50% yield) as a TFA salt.

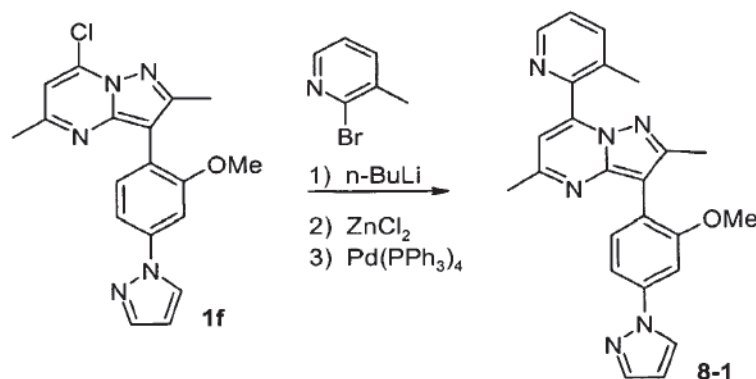
The following table summarizes the compounds of Example 7. By varying the amine employed in the reductive amination step above, Cmpds 7-5 and 7-6, included in the table, were synthesized by the methods of Step 7E:



Cmpd	R ₂	MW	MS	t _R	HPLC Method
7-1		425.49	425	5.41	2
7-2		443.94	444.1	1.15	4
7-3		434.50	435.4	7.05	2
7-4		506.82	509.2	5.13	2
7-5		524.69	525.2	5.48	2
7-6		496.612	497.2	5.18	2
7-7		489.58	490.2	4.94	

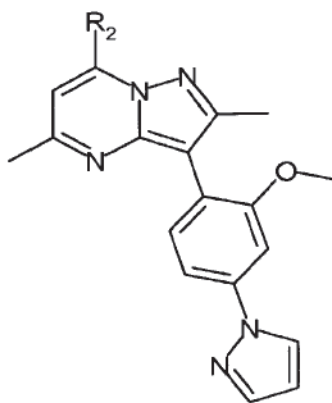
EXAMPLE 8

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

**5 Step 8A:**

To a solution of 2-bromo-3-methylpyridine (4.85 g, 28.2 mmol) in dry THF (8.0 mL) cooled to -70°C was added n-BuLi (1.6 M solution in hexane, 17.6 mL, 28.2 mmol) dropwise. The reaction mix was stirred at -70°C for 30 min, then ZnCl_2 (0.5 M solution in THF, 66.0 mL, 34 mmol) was added over 5 min. The mixture was
 10 allowed to warm to 0°C over 1 hr, then Cmpd **1f** (1.66 g, 4.70 mmol) and tetrakis(triphenylphosphine)palladium(0) (326 mg, 0.28 mmol) were added. The mixture was then heated to reflux for 4 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,
 15 concentrated, and the residue was chromatographed on silica gel using 1:3 hexanes/ethyl acetate to give **8-1** free base (1.6 g, 83 %) as a yellow solid. To a solution of **8-1** (1.6 g, 3.9 mmol) in 7:1 ethyl acetate/chloroform (100 mL) was added hydrogen chloride (4.0 mL of a 2.0 M solution in ether, 8.0 mmol) at 0°C . The suspension was diluted with ether, then the solid was collected on a fritted glass filter
 20 and rinsed with ether to obtain **8-1** HCl salt (1.7 g, 98 %) after drying under high vacuum.

Depending on the halide employed in Step 8A above, the compounds of the following table were synthesized:



Cmpd	R ₂	MW	MS	t _R ⁺
8-1		410.48	411	5.400
8-2		410.48	411	5.770
8-3		426.48	427	5.690
8-4		440.51	441	6.240
8-5		399.456	399	4.130
8-6		426.478	426	6.410
8-7		396.452	396	5.720

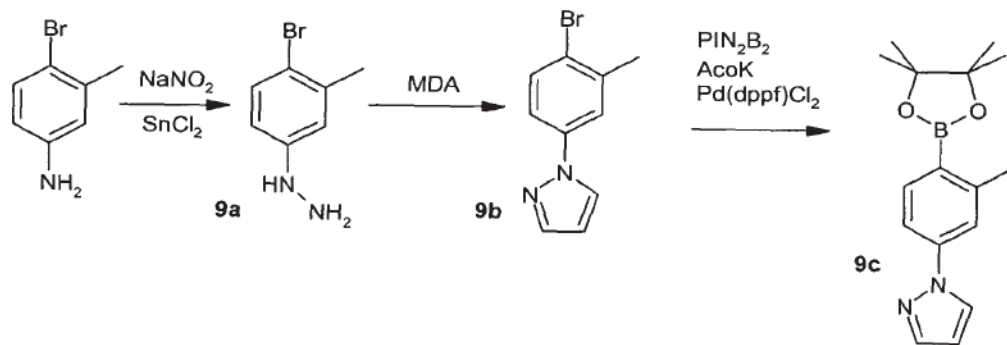
Cmpd	R ₂	MW	MS	t _R
8-8		396.452	396	4.940
8-9		410.479	410	5.640
8-10		375.474	375	6.260
8-11		426.478	426	5.850
8-12		410.479	410	4.700

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 9

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

5



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 H₂O) 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 H₂O to afford 4-bromo-3-methylphenylhydrazine hydrochloride (Cmpd **9a**, 20 g) as a tan solid.

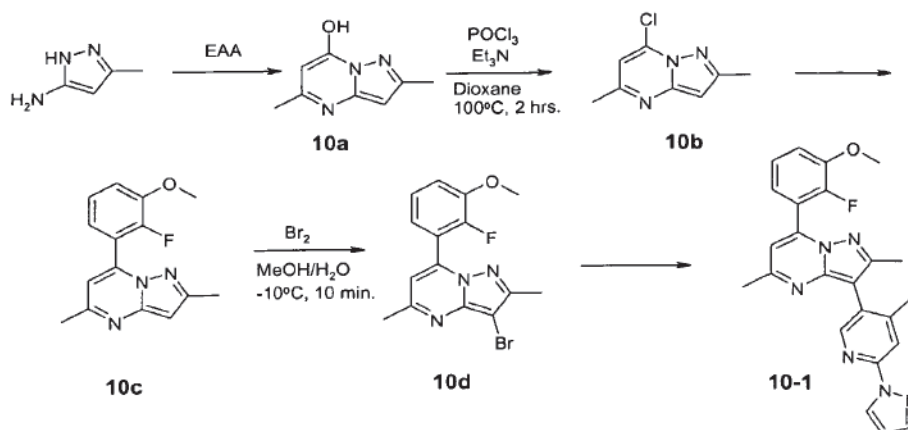
Step 9B:

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****5 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.

10 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.

20 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.

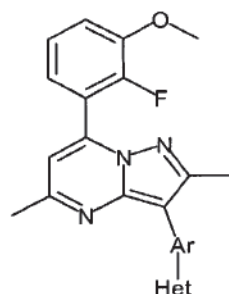
Step 10D:

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.

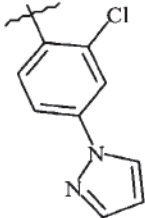
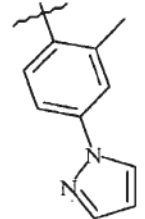
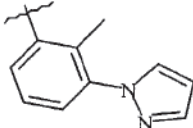
Step 10E:

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:



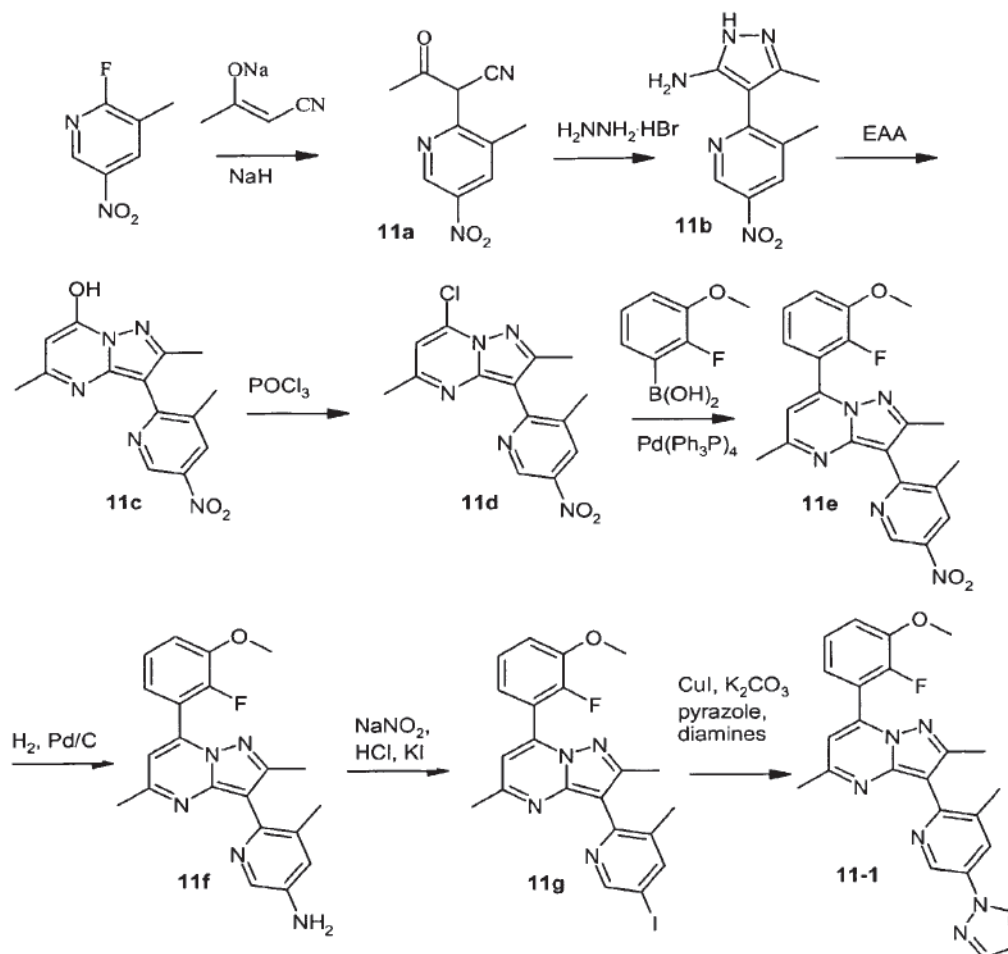
Cmpd	AR-HET	MW	MS	t _R ⁺
10-1		428.469	429	8.110

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

**5 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:

5 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:

10 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:

15 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
20 yellow solid.

Step 11E:

25 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
5 purged with nitrogen and filtered. The filtrate was concentrated to provide **11f** (260 mg, 94% yield) as a yellow oil.

Step 11G:

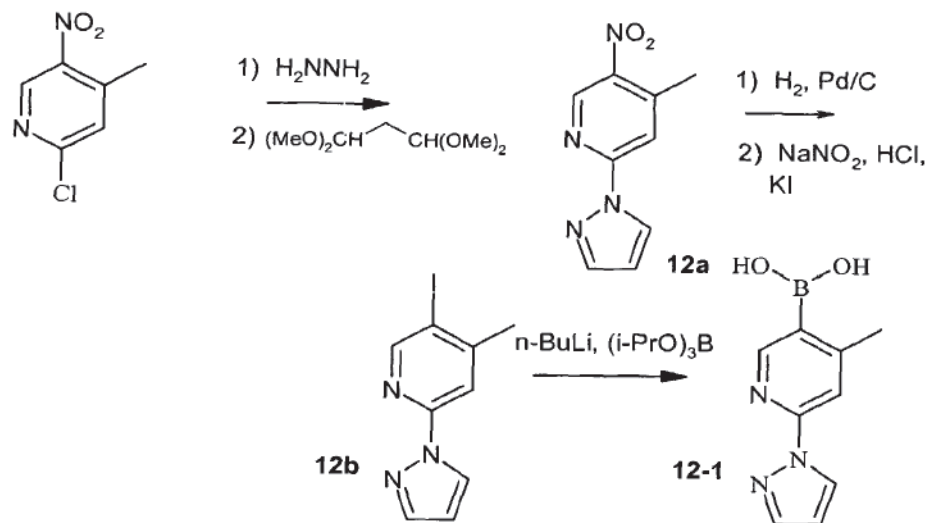
A solution of sodium nitrite (60 mg, 0.87 mmol, 1.3 eq) in water (10 mL) was added dropwise to an ice-cold solution of **11f** (260 mg, 0.69 mmol, 1.0 eq) in 4N
10 hydrochloric acid (5 mL). The mixture was stirred at 0 °C for 1 hr, followed by addition of 10 mL of half-saturated aqueous potassium iodide. 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
15 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
20 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)
25 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-NITROPYRIDINE

Step 12A:

- 5 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.
- 10 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,
- 15 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
- 20 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

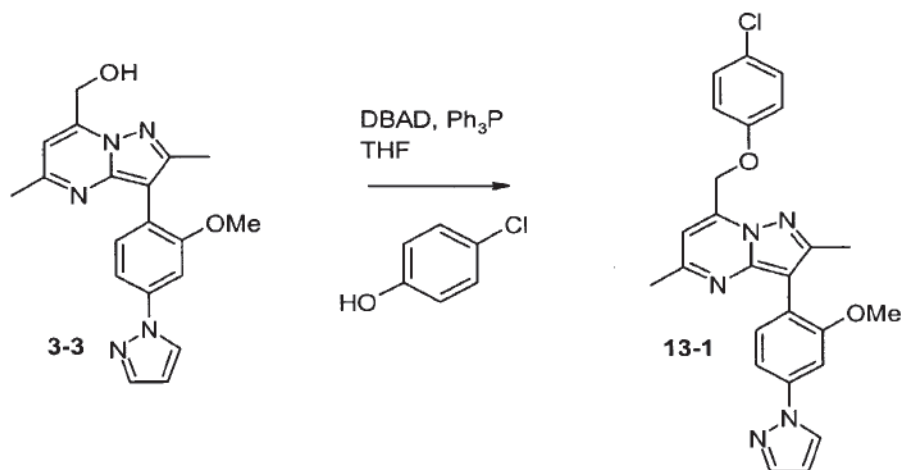
to 0 °C, then treated dropwise with a solution of sodium nitrite (835 mg, 12 mmol, 1.1 eq) in 2 mL water. The mixture was stirred at 0 °C for 1 hr, then 2 mL of half-saturated potassium iodide was added and the mixture was stirred at RT for 22 hr. Saturated aqueous sodium bicarbonate solution was added, then the mixture was extracted with 5 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:

10 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 15 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 20 red solid.

EXAMPLE 13

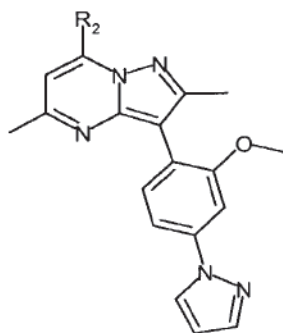
7-(4-CHLORO-PHENOXYMETHYL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



5 **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
 10 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:

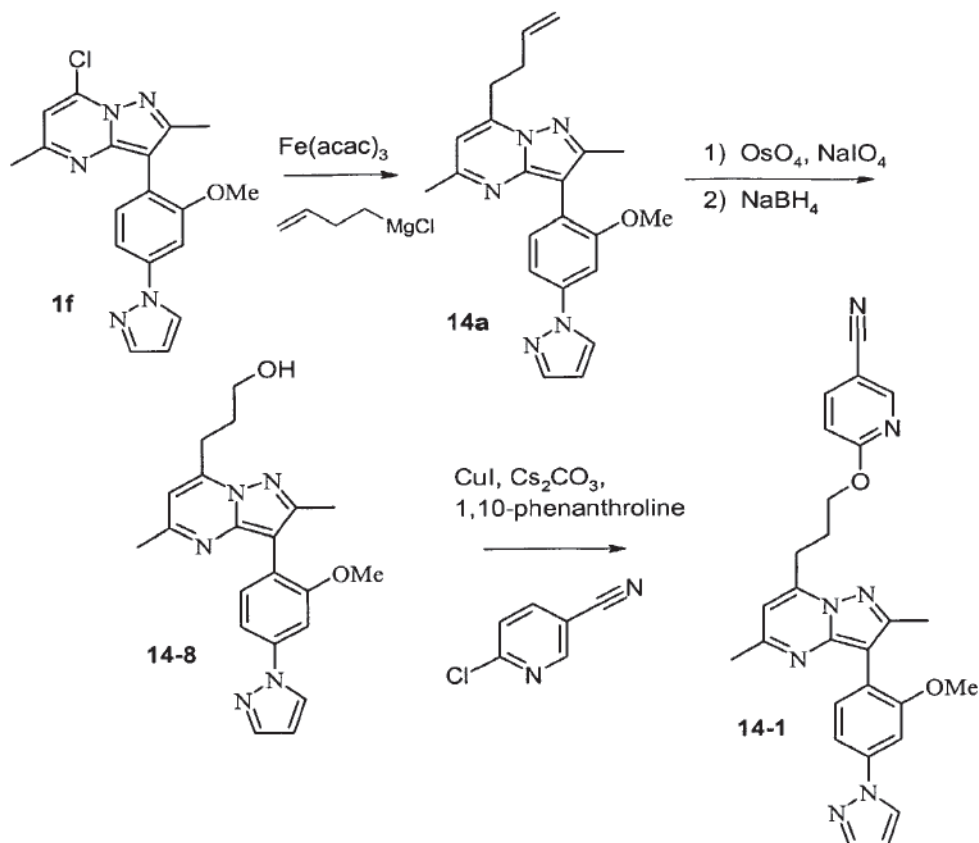


Cmpd	R ₂	MW	MS	t _R *
13-1		459.935	460	9.090
13-2		493.487	494	7.690
13-3		477.925	478	9.210
13-4		450.5	451	7.850
13-5		477.925	478	9.170
13-6		425.49	426	8.420

* 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



5 **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).

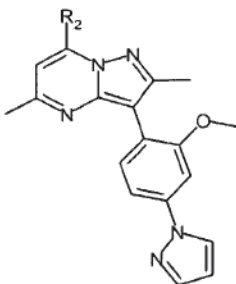
Step 14B:

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).

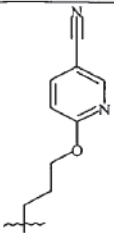
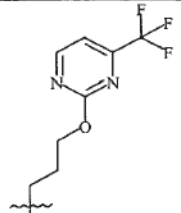
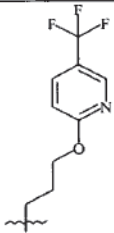
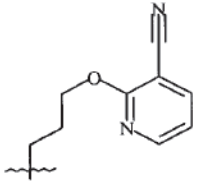
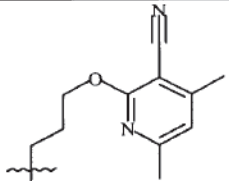
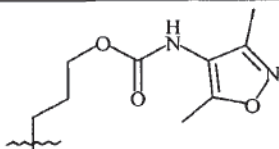
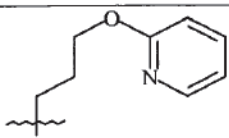
Step 14C:

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 addition to Cmpd **14-1** were synthesized and purified by preparative LC-MS.



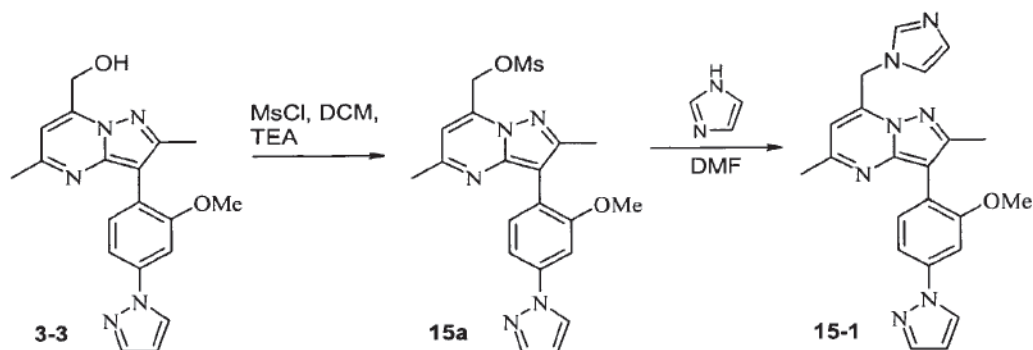
Cmpd	R ₂	MW	MS	t _R ⁺
14-1		377.446	377	5.170

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

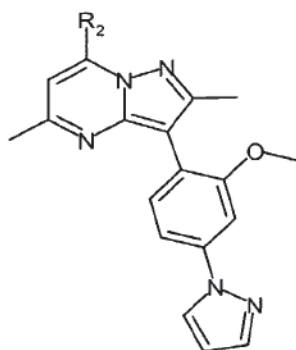
**5 Step15A:**

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:

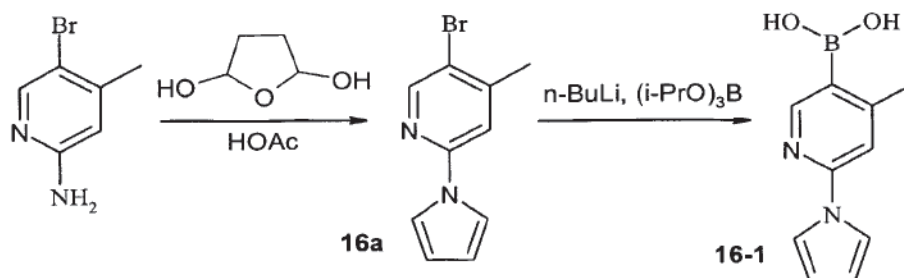
Potassium carbonate (20 mg, 0.14 mmol, 2.6 eq) and imidazole (20 mg, 0.30 mmol, 5.5 eq) were added to a solution of **15a** (23 mg, 0.054 mmol, 1 eq) in DMF (1 mL). The reaction mixture was stirred at RT for 16 hr, then methanol (1 mL) was added and the reaction mixture was purified directly by preparative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

- 5 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.

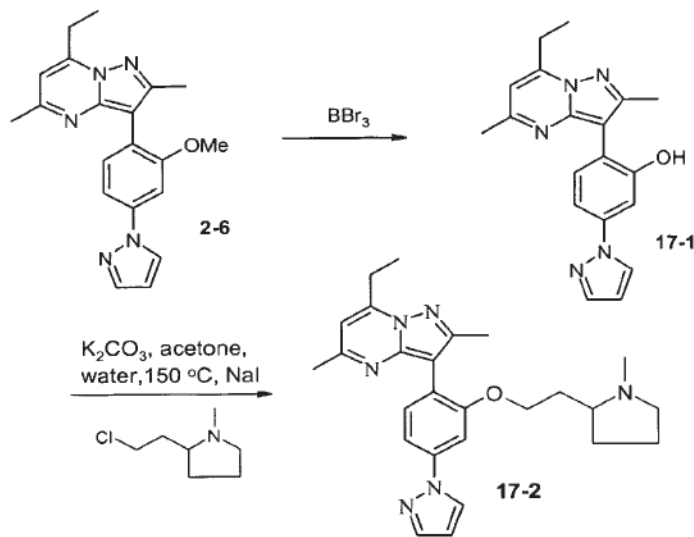
10 **Step 16B:**

- 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
- 15 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.

20

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

**5 Step 17A:**

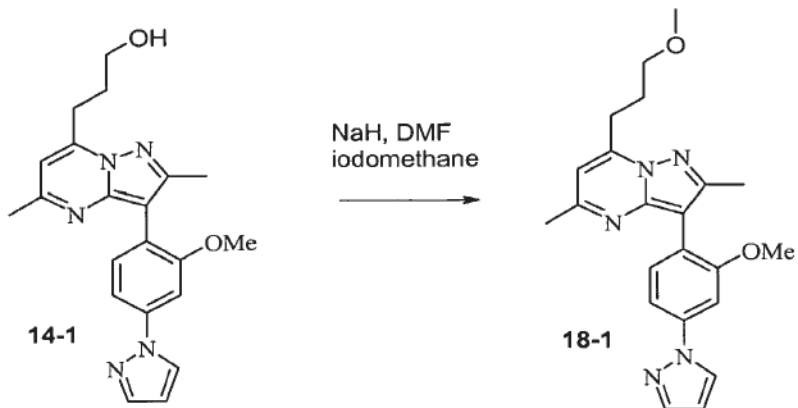
To a solution of Cmpd **2-6** (350 mg) in chloroform (5 mL) was added BBr_3 (1.0 M in DCM, 5 mL.) The mixture was stirred overnight at room temperature and quenched with water. The mixture was extracted with chloroform (2x 10 mL), then the combined organic extracts were dried over sodium sulfate, filtered, 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 $[\text{MH}]^+$; 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



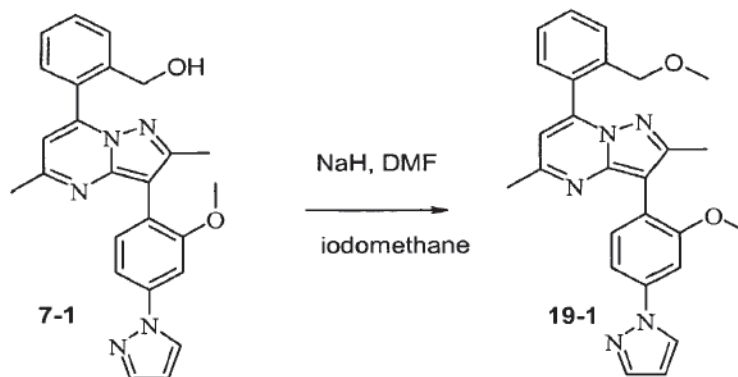
5 **Step 18A:**

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, methyl iodide (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

10 TFA salt; MW: 391.47 LC/MS: 391 [MH]⁺; t_R: 7.050, Anal. Meth. 2.

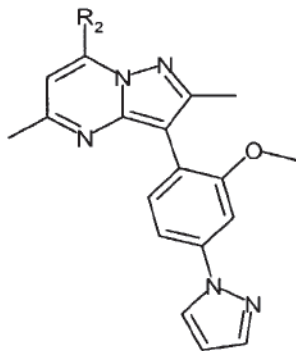
EXAMPLE 19

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

**5 Step 19A:**

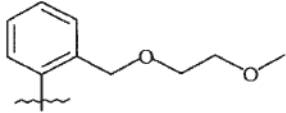
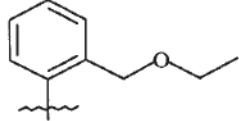
The procedure of Example 18 was followed using Cmpd **7-1** as starting material

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



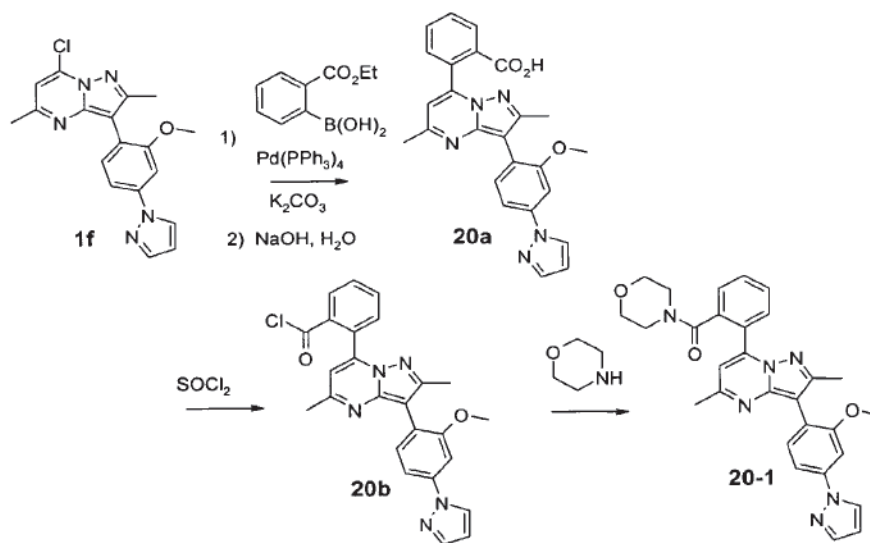
10

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



5 Step 20A:

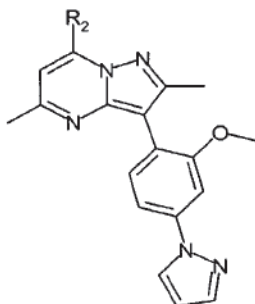
A mixture of Cmpd **1f** (710 mg, 2.0 mmol), (2-ethoxycarbonyl)phenylboronic acid (470 mg, 2.4 mmol), tetrakis (triphenylphosphine)palladium(0) (116 mg, 0.1 mmol), and potassium carbonate (550 mg, 4.0 mmol) was heated in 9:1 dioxane/water (10 mL) at 100 °C for 2.5 hr. Sodium hydroxide solution (3N, 10 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.

5 **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:

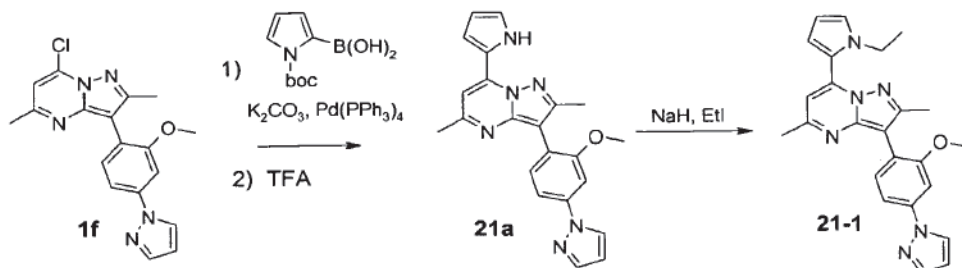


Cmpd	R ₂	MW	MS	t _R *
20-1		508.579	508	6.180
20-2		506.607	506	7.050
20-3		492.58	492	6.710
20-4		491.552	491	5.840

* 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

5 Step 21A:

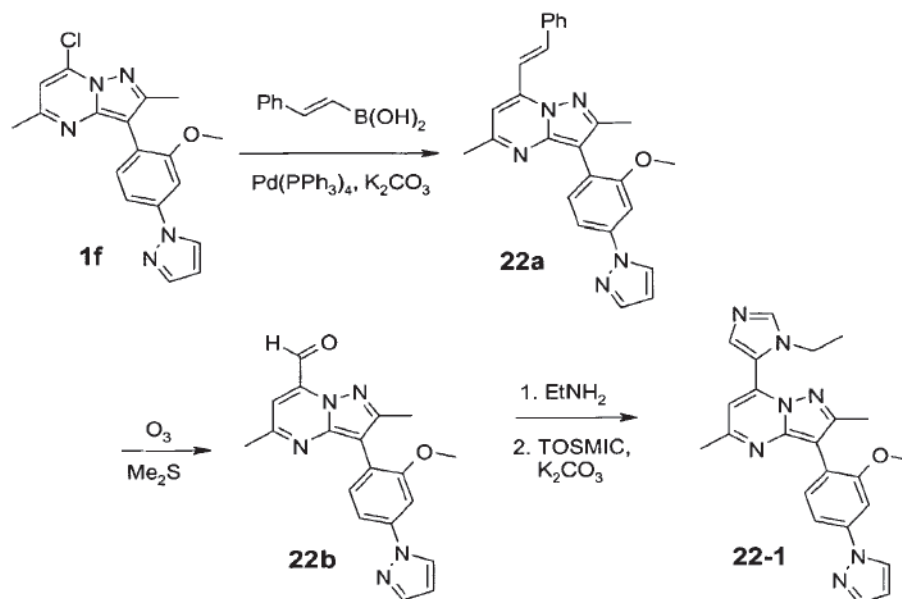
A mixture of Cmpd **1f** (210 mg, 0.6 mmol), N-Boc-pyrrole-2-boronic acid (158 mg, 0.75 mmol), tetrakis(triphenylphosphine)palladium(0) (40mg, 0.035 mmol), and potassium carbonate (166 mg, 1.2 mmol) was heated in 9:1 dioxane/water (5 mL) at 110 °C for 3 hr in a sealed tube. The cooled mixture was concentrated, then water
 10 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
 15 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
 20 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
 25 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

**5 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
 10 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:

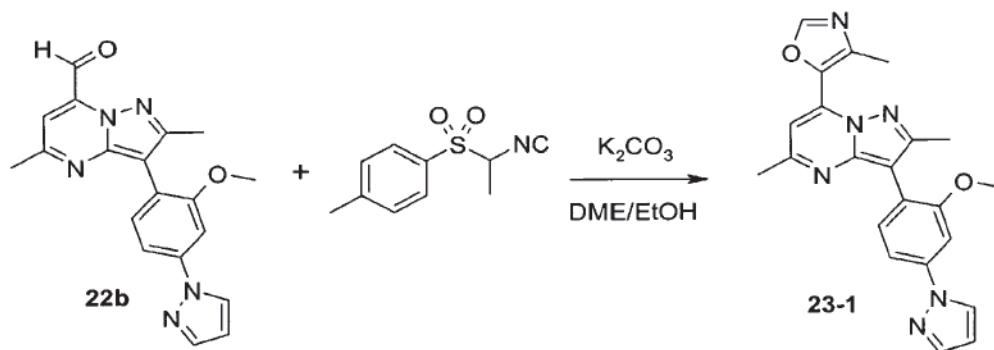
An ozone/oxygen mixture was bubbled through a solution of **22a** (1.60 g, 3.8 mmol) in dry 2:1 DCM/methanol (20 mL) at – 70 °C for 8 minutes. Dimethyl sulfide (1.5 mL) was added and the mixture was stirred and allowed to warm to RT over 16 hr. The solvent was evaporated and the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent, providing Cmpd **22b** (1.0 g, 76 %
 15 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

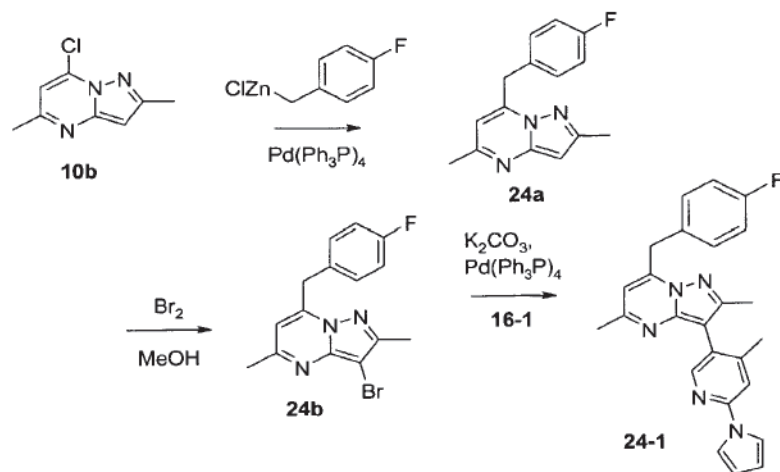
3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(4-METHYL-OXAZOL-5-YL)-
PYRAZOLO[1,5-A]PYRIMIDINE



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

**5 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.

15 Step 24B:

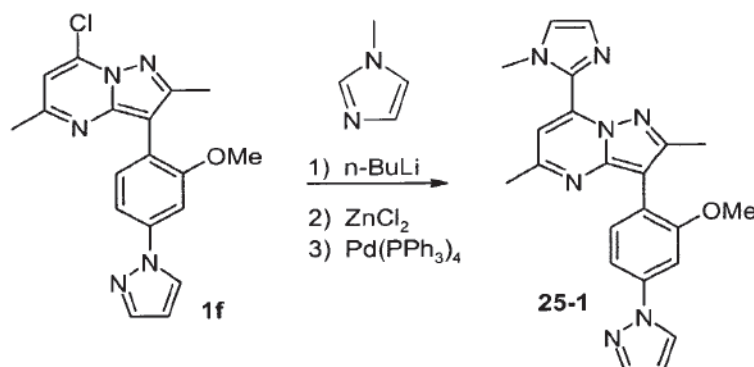
Compound **24a** (1.0 g, 3.9 mmol) was dissolved in 15 mL methanol. Bromine (0.62 g, 3.9 mmol) was added dropwise to the solution, resulting in formation of a white precipitate. The solid was collected on a fritted glass filter and rinsing with methanol. This compound was further purified by silica gel 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:

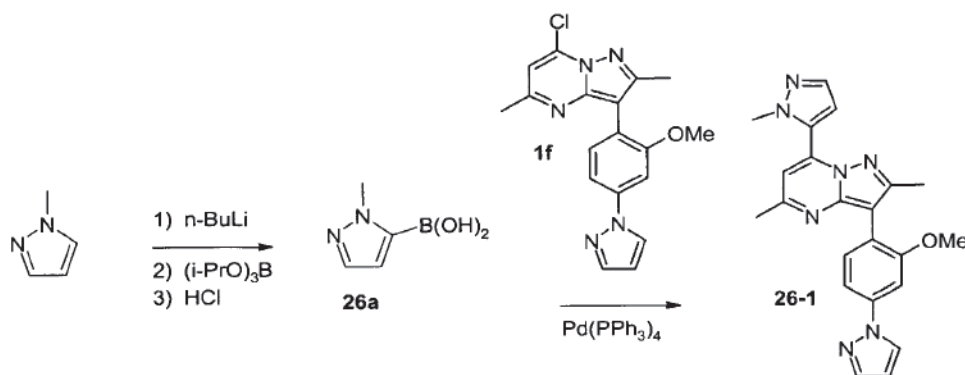
To a solution of 1-methylimidazole (246 mg, 3.0 mmol) in dry THF (3 mL) cooled to -70 °C was added *n*-BuLi (2.5 M solution in hexane, 1.7 mL, 4.2 mmol) dropwise. The reaction mix was stirred at -70 °C for 10 min, then ZnCl₂ (0.5 M solution in THF, 20 mL, 10 mmol) was added over 5 min. The mixture was 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.

5

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



10 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
 15 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:

20 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
 25 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

5 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
10 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 1-10 μ g cell membranes from cells stably transfected with
15 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 [¹²⁵I] tyrosine - sauvagine (final concentration ~150 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 mL of a cell
20 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 ¹²⁵I) is counted using a scintillation counter. All radioligand binding data may be analyzed using the non-linear least-squares curve-fitting programs Prism
25 (GraphPad Software Inc) or XLfit (ID Business Solutions Ltd).

EXAMPLE 28

CRF-STIMULATED ADENYLATE CYCLASE ACTIVITY

The compounds of the present invention may also be evaluated by
30 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

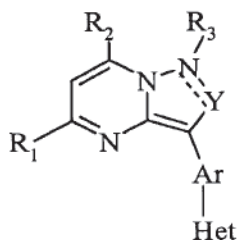
generally described by Battaglia et al. (*Synapse* 1:572, 1987) with modifications to adapt the assay to whole cell preparations.

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
5 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
10 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.

15 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;

R₁ is hydrogen, alkyl, substituted alkyl, heteroaryl, substituted heteroaryl, -NH₂, or halogen;

R₂ is alkyl, substituted alkyl, -C(O)NR₇R₈, 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;

R₃ is null, hydrogen, or alkyl;

Y is =(CR₄)- or -(C=O)-;

R₄ is hydrogen, alkyl, substituted alkyl, thioalkyl, alkylsulfinyl, or alkylsulfonyl;

Ar is phenyl, phenyl substituted with 1 or 2 R₅, pyridyl or pyridyl substituted with 1 or 2 R₅;

R₅ 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 R₆;

R₆ at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen; and

R₇ and R₈ are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, arylalkyl, substituted arylalkyl, heterocyclealkyl or substituted heterocyclealkyl; or

R₇ and R₈ 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:

R₁ is hydrogen, alkyl or substituted alkyl;
R₃ is null;
Y is =(CR₄)-;
R₄ is hydrogen, alkyl or substituted alkyl;
Ar is phenyl substituted with one R₅;
R₅ is alkyl, substituted alkyl, alkoxy or substituted alkoxy; and
Het is heteroaryl.

14. A compound according to claim 13,

wherein:

R₁ is lower alkyl;
R₄ is lower alkyl;
R₅ is alkoxy; and
Het is pyrazolyl.

15. A compound according to claim 14,

wherein:

R₁ is methyl;
R₄ is methyl; and
R₅ is methoxy.

16. A compound according to claim 15,

wherein:

R₂ is alkyl, substituted arylalkyl, substituted aryl, heteroaryl, substituted heteroaryl, substituted heteroaryloxyalkyl, heteroarylalkyl or substituted heteroarylalkyl.

17. A compound according to claim 16,

wherein:

R₂ 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.

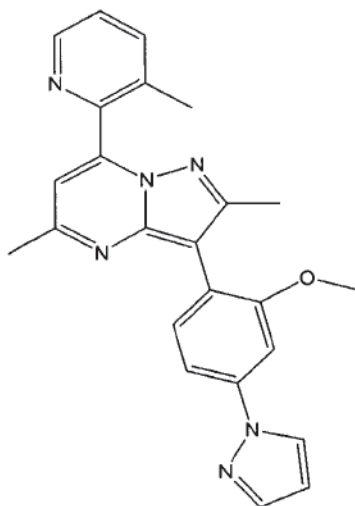
20. A compound according to claim 19,
wherein:

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. 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
Y	US 6 313 124 B1 (HE LIQI ET AL) 6 November 2001 (2001-11-06) cited in the application column 10, lines 24 ff	1-30
Y	WO 97/29109 A (JANSSEN PHARMACEUTICA N.V; NEUROCRINE BIOSCIENCES INC; CHEN, CHEN; WEB) 14 August 1997 (1997-08-14) cited in the application claim 1 and p.5, line 26	1-30

☐ 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.
- *&* document member of the same patent family

Date of the actual completion of the international search

20 June 2005

Date of mailing of the international search report

27/06/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Wolf, C

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. ☒ 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. Application No
PCT/IB2004/004234

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6313124	B1	06-11-2001	US 6124289 A 26-09-2000
			AT 264860 T 15-05-2004
			AU 748818 B2 13-06-2002
			AU 2478799 A 16-08-1999
			BR 9908206 A 05-12-2000
			CA 2314613 A1 05-08-1999
			CN 1289335 A ,C 28-03-2001
			CN 1542010 A 03-11-2004
			DE 69916578 D1 27-05-2004
			DE 69916578 T2 31-03-2005
			DK 1049699 T3 05-07-2004
			EP 1344779 A1 17-09-2003
			EP 1049699 A1 08-11-2000
			ES 2218991 T3 16-11-2004
			JP 2002501922 T 22-01-2002
			NZ 505079 A 29-08-2003
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			PL 342183 A1 21-05-2001
			PT 1049699 T 31-08-2004
			SI 1049699 T1 31-10-2004
			TW 520372 B 11-02-2003
			WO 9938868 A1 05-08-1999
			US 2003008885 A1 09-01-2003
			BR 9710544 A 17-08-1999
			CA 2259583 A1 29-01-1998
			CN 1327793 A 26-12-2001
			CN 1388126 A 01-01-2003
			CN 1225637 A ,C 11-08-1999
			CZ 9900184 A3 17-11-1999
			EA 4403 B1 29-04-2004
			EE 9900019 A 16-08-1999
			HR 970413 A1 31-10-1998
			JP 2002513382 T 08-05-2002
			JP 2005097257 A 14-04-2005
			NO 990264 A 10-03-1999
			NZ 333777 A 28-07-2000
			PL 331523 A1 19-07-1999
			SI 9720045 A 31-10-1999
			SK 9799 A3 01-04-2005
			US 6136809 A 24-10-2000
			US 6060478 A 09-05-2000
			US 6191131 B1 20-02-2001
			US 6358950 B1 19-03-2002
WO 9729109	A	14-08-1997	AU 713673 B2 09-12-1999
			AU 1599197 A 28-08-1997
			BG 102349 A 26-02-1999
			BR 9707391 A 20-07-1999
			CA 2233285 A1 14-08-1997
			CN 1205009 A 13-01-1999
			CZ 9802445 A3 14-10-1998
			DE 880523 T1 04-07-2002
			EA 980394 A1 29-10-1998
			EE 9800124 A 15-10-1998
			WO 9729109 A1 14-08-1997
			EP 0880523 A1 02-12-1998
			ES 2168237 T1 16-06-2002
			HU 9900575 A2 28-06-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No
PCT/IB2004/004234

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9729109	A	ID 15905 A	14-08-1997
		JP 3356291 B2	16-12-2002
		JP 2000503661 T	28-03-2000
		JP 2002121194 A	23-04-2002
		NO 981357 A	03-08-1998
		NZ 330119 A	28-02-2000
		PL 327284 A1	07-12-1998
		SK 106398 A3	02-12-1998
		TR 9800792 T2	21-07-1998
		TW 449599 B	11-08-2001
		US 2003125341 A1	03-07-2003
		US 2004127483 A1	01-07-2004
		ZA 9700989 A	06-08-1998

Form PCT/ISA/210 (patent family annex) (January 2004)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: JIARONG L. LAMQUIZ
WILSON SONSINI
650 PAGE MILL ROAD
PALO ALTO, CA 94304

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing (day/month/year) DEC 17 2021
Applicant's or agent's file reference 50535-719601	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 21/45780	International filing date (day/month/year) 12 August 2021 (12.08.2021)
Applicant SPRUCE BIOSCIENCES, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.
- Filing of amendments and statement under Article 19:**
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):
- When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.
- How?** Directly to the International Bureau preferably through ePCT, or on paper to:
The International Bureau of WIPO, 34, chemin des Colombettes, 1211 Geneva 20, Switzerland

For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to any protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:**
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of **18 months from the priority date**, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **22 months from the priority date**, the applicant may request that a **supplementary international search** be carried out by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriguez Telephone No. PCT Helpdesk: 571-272-4300
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Form PCT/ISA/220 (revised January 2020)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 50535-719601		FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US 21/45780	International filing date (day/month/year) 12 August 2021 (12.08.2021)	(Earliest) Priority Date (day/month/year) 12 August 2020 (12.08.2020)	
Applicant SPRUCE BIOSCIENCES, INC.			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

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.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2019)

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.

* 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

21 November 2021

Date of mailing of the international search report

DEC 17 2021

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Kari Rodriguez

Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: JIARONG L. LAMQUIZ
WILSON SONSINI
650 PAGE MILL ROAD
PALO ALTO, CA 94304

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

DEC 17 2021

Applicant's or agent's file reference
50535-719601

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 21/45780

International filing date (day/month/year)

12 August 2021 (12.08.2021)

Priority date (day/month/year)

12 August 2020 (12.08.2020)

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

IPC - A61B 18/14; A61B 18/02; A61B 18/04 (2021.01)

CPC - A61N 1/36117; A61B 18/04; A61B 18/1492

Applicant SPRUCE BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

21 November 2021

Authorized officer

Kari Rodriguez

PCT Help Desk

Telephone No. 571-272-4300

Form PCT/ISA/237 (cover sheet) (revised January 2019)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 21/45780

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5-8, 16-37, 41-66

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 5-8, 16-37, 41-66 are so unclear that no meaningful opinion could be formed (*specify*):

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 5-8, 16-37, 41-66

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

Form PCT/ISA/237 (Box No. III) (revised January 2019)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 21/45780

Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement			
1. Statement				
Novelty (N)	Claims	1-4, 9-15, 38-40	YES	
	Claims	NONE	NO	
Inventive step (IS)	Claims	1-4, 9-15, 38-40	YES	
	Claims	NONE	NO	
Industrial applicability (IA)	Claims	1-4, 9-15, 38-40	YES	
	Claims	NONE	NO	
2. Citations and explanations:				
<p>Claims 1-4, 9-15 and 38-40 meet the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the subject matter claimed.</p> <p>Regarding Claim 1, US 2017/0333126 A1 to Medtronic Ardian Luxembourg S.a.r.l. (hereinafter Medtronic) discloses a method of treating polycystic ovary syndrome (abstract), but does not disclose 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.</p> <p>US 2010/0222339 A1 to Chen et al. (hereinafter Chen) discloses a CRF1 antagonist (abstract), but does not disclose 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.</p> <p>US 2018/0110554 A1 to Ziva Medicinal, Inc (hereinafter Ziva) discloses a method of treating polycystic ovary syndrome (abstract), but does not disclose 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.</p> <p>Regarding Claim 2, Medtronic discloses a method of treating polycystic ovary syndrome (abstract), but does not disclose a method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a CRF1 antagonist.</p> <p>Chen discloses a CRF 1 antagonist (abstract), but does not disclose a method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a CRF1 antagonist.</p> <p>Ziva discloses a method of treating polycystic ovary syndrome (abstract), but does not disclose a method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a CRF1 antagonist.</p> <p>Regarding Claims 3-4 and 9-15, these are dependent claims depending from claims 1-2 and therefore, meet the criteria set forth in PCT Article 33(2)-(3).</p> <p>Regarding Claim 38, Medtronic discloses a method of treating polycystic ovary syndrome (abstract), but does not disclose 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.</p> <p>Chen discloses a compound of formula 3 (para [0144]), but does not disclose 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.</p> <p>Ziva discloses a method of treating polycystic ovary syndrome (abstract), but does not disclose 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.</p> <p>Regarding Claim 39, Medtronic discloses a method of treating polycystic ovary syndrome (abstract), but does not disclose 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.</p> <p>Chen discloses a compound of formula 3 (para [0144]), but does not disclose 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.</p> <p>--continued on supplemental page--</p>				

Form PCT/ISA/237 (Box No. V) (revised January 2019)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 21/45780

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

--continued from Box No. V--

Ziva discloses a method of treating polycystic ovary syndrome (abstract), but does not disclose 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.

Regarding Claim 40, this is a dependent claim depending from claims 38-39 and therefore, meets the criteria set forth in PCT Article 33(2)-(3).

Claims 1-4, 9-15 and 38-40 have industrial applicability as defined by PCT Article 33(4) because the subject matter could be made or used in industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X18287	FOR FURTHER ACTION		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2009/058722	International filing date (day/month/year) 29/09/2009	(Earliest) Priority Date (day/month/year) 02/10/2008	
Applicant ELI LILLY AND COMPANY			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1
☒ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/058722

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04

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)
C07D

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/036579 A1 (LILLY CO ELI [US]; CHEN ZHAOGEN [US]; HAMDOUCHI CHAFIQ HAMDOUCHI [US];) 27 March 2008 (2008-03-27) cited in the application Pages 30-32, 36-38 examples 4,14,16,16/alternate preparation,17	1-18

☐ 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

"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.

"S" document member of the same patent family

Date of the actual completion of the international search

18 January 2010

Date of mailing of the international search report

25/01/2010

Name and mailing address of the ISA/

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Authorized officer

Lange, Tim

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/058722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008036579 A1	27-03-2008	AR 062886 A1	10-12-2008
		AU 2007297421 A1	27-03-2008
		CA 2663511 A1	27-03-2008
		CL 26932007 A1	18-04-2008
		CN 101516887 A	26-08-2009
		CR 10682 A	13-08-2009
		EA 200970303 A1	30-10-2009
		EP 2094709 A1	02-09-2009
		KR 20090052366 A	25-05-2009

Form PCT/ISA/210 (patent family annex) (April 2005)

CRF1 receptor antagonist for the treatment of congenital adrenocortical hyperplasia

Abstract

translated from Japanese

CRF1 receptor antagonists directly inhibit ACTH release in patients with CAH, thereby allowing normalization of androgen production while using lower, more physiological doses of hydrocortisone, thus reducing treatment-related side effects. Has the ability to reduce. In one embodiment, a method for treating CAH is provided by administering to a subject in need an effective amount of a CRF1 antagonist, including but not limited to bedtime administration. The

Images (6)



Classifications

A61K31/519 Pyrimidines; Hydrogenated pyrimidines, e.g. trimethoprim ortho- or peri-condensed with heterocyclic rings

[View 4 more classifications](#)

JP2017503030A

Japan

[Download PDF](#)
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[Images](#)

Other languages: Japanese

Inventor: ディミトリイ, グリゴリアディス, ディミトリイ, グリゴリアディス,

Worldwide applications

2015 CA MX JP WO AU EP NZ CA KR RU HR CN CN RU US
2016 IL 2018 US 2019 JP 2020 JP AU US 2021 US
IL JP

Application JP2016565135A events

2014-01-21 Priority to US2014019299A1P

2015-01-21 Application filed by ニューロクライン バイオサイエンス, インコーポレイテッド, ニューロクライン バイオサイエンス, インコーポレイテッド

2017-01-26 Publication of JP2017503030A

2018-03-01 Publication of JP2017503030A5

2019-10-02 Application granted

2019-10-02 Publication of JP6865625B2

Status Active

2035-01-21 Anticipated expiration

[Show all events](#) ▼

Info: Patent citations (57), Cited by (9), Legal events, Similar documents, Priority and Related Applications

External links: Espacenet, Global Dossier, Discuss

Claims (21)

[Hide Dependent](#) ▲
translated from Japanese

A method for treating congenital adrenocortical hyperplasia (CAH) by administering to a subject in need a CRF₁ receptor antagonist having a dissociation half-life of greater than 30 minutes. The method of claim 1, wherein the CRF₁ receptor antagonist has a dissociation half-life of greater than 40 minutes. The method of claim 1, wherein the CRF₁ receptor antagonist has a dissociation half-life of greater than 50 minutes. Said CRF₁ receptor antagonist is compound 1 (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methyloxy) phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine). The CRF₁ receptor antagonists include NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6- The method according to claim 1, which is trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine), or DMP904. 6. The method of any one of claims 1-5, wherein the CRF₁ receptor antagonist is administered at bedtime. 6. The method of any one of claims 1-5, wherein the CRF₁ receptor antagonist is administered during or prior to ACTH release with a predicted circadian rhythm. 8. The method of claim 7, wherein the CRF₁ receptor antagonist is administered 3-4 hours prior to ACTH release with a predicted circadian rhythm. A method for reducing the levels of 17-OHP and ACTH in a subject having congenital adrenocortical hyperplasia (CAH) comprising administering to the subject a CRF₁ receptor antagonist at bedtime, including the method. 10. The method of claim 9, wherein the CRF₁ receptor antagonist is administered at or prior to ACTH release with a predicted circadian rhythm. 10. The method of claim 9, wherein the CRF₁ receptor antagonist is administered 3-4 hours prior to ACTH release with a predicted circadian rhythm. Said CRF₁ receptor antagonist is compound 1 (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methyloxy) phenyl]-N-[(1S)-1-(3-methyl- The method according to any one of claims 9 to 11, which is 1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine). The CRF₁ receptor antagonists include NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6- The method according to any one of claims 9 to 11, which is (trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine) or DMP904. A CRF₁ receptor antagonist for use in treating congenital adrenal hyperplasia (CAH), wherein the CRF₁ receptor antagonist has a dissociation half-life greater than 30 minutes, CRF₁ receptor antagonist. The CRF₁ receptor antagonist has a dissociation half-life greater than 40 minutes, CRF₁ receptor antagonist of claim 14. The CRF₁ receptor antagonist has a dissociation half-life greater than 50 minutes, CRF₁ receptor antagonist of claim 14. Said CRF₁ receptor antagonist is compound 1 (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methyloxy) phenyl]-N-[(1S)-1-(3-methyl- The CRF₁ receptor antagonist according to claim 14, which is 1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine). The CRF₁ receptor antagonists include NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6- The CRF₁ receptor antagonist according to claim 14, which is (trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine) or DMP904. The CRF₁ receptor antagonist is suitable for administration at bedtime, CRF₁ receptor antagonist

according to any one of claims 14 to 18. The CRF₁ receptor antagonist is suitable for administration at the time of ACTH release by circadian rhythms predicted or before that, CRF₁ receptor antagonist according to any one of claims 14 to 18. The CRF₁ receptor antagonist is suitable for administration to 3-4 hours prior to ACTH release by circadian rhythm expected, CRF₁ receptor antagonist according to any one of claims 14 to 18.

Description

translated from Japanese

(background)

(Technical field)

Compositions and methods for treating congenital adrenocortical hyperplasia are described herein.

(Description of related technology)

Congenital adrenocortical hyperplasia (CAH) is a group of autosomal recessive genetic disorders that produce little or no cortisol biosynthesis. The most frequent form of the disease is a 21-hydroxylase deficiency caused by mutations in the CYP21A2 gene located on chromosome 6p21, accounting for about 95% of CAH cases (for review see, for example, Speiser et al., *Int. J. Pediatr. Endocrinol.* 2010; 494173 (2010)). These mutations can range from a complete loss of enzyme activity required for cortisol synthesis in the adrenal cortex to a range of partial losses resulting in disease severity that is a direct consequence of certain mutations. This continuous form of 21-hydroxylase deficiency is more commonly known as salt loss and simple maleized forms (grouped as classical CAH) and non-classical CAH (NCCAH) or "late-onset" CAH. It has been broadly classified into a mild form, which is usually diagnosed in late childhood or early adulthood. Nonclassical CAH patients have either homozygous or complex heterozygotes, often with a classical CAH allele. These patients have sufficient enzymatic activity (> 20-50% normal), so that they have no salt loss or cortisol deficiency, have normal external genitals at birth, and many it remains asymptomatic throughout life (Trap et al., *Steroids* 77 (4); 342-46 (2012)). In the less frequent form of the disease (which accounts for 5% of cases), mutations in the 11 β -hydroxylase gene CYP11B1 result in CAH (11 β -OH CAH).

Both genetic variations result in congenital adrenocortical hyperplasia, cortisol deficiency and excessive adrenocorticotrophic hormone (ACTH) production, along with androgen overproduction. These patients require lifelong management with glucocorticoids and the problems associated with such treatment. Thus, treatment regimens are very necessary to improve health, well-being, quality of life, and to manage associated disorders in patients with CAH.

Speiser et al., *Int. J. Pediatr. Endocrinol.* 2010; 494173 (2010) Trapp et al., *Steroids* 77 (4); 342-46 (2012)

(Summary)

Corticotropin releasing factor (CRF) activates CRF₁ receptor, a class B G protein coupled receptor (GPCR). CRF₁ antagonists directly inhibit ACTH release in patients with CAH, thereby allowing normalization of androgen production while using lower, more physiological doses of hydrocortisone and reducing treatment-related side effects Have

In one embodiment, a method for treating CAH is provided by administering to a subject in need an effective amount of a CRF₁ antagonist, including but not limited to bedtime administration, is done.

In a more specific embodiment, the CRF₁ antagonist has a dissociation half-life ($t_{1/2}$) greater than 30 minutes, and in another embodiment greater than 40 minutes, and in another embodiment greater than 50 minutes. Have

Embodiment 1 A method for treating congenital adrenocortical hyperplasia (CAH) by administering to a subject in need a CRF₁ receptor antagonist having a dissociation half-life of greater than 30 minutes.

Embodiment 2 The method of embodiment 1, wherein the CRF₁ receptor antagonist has a dissociation half-life of greater than 40 minutes.

Embodiment 3 The method of embodiment 1, wherein the CRF₁ receptor antagonist has a dissociation half-life of greater than 50 minutes.

Embodiment 4 The CRF₁ receptor antagonist is compound I (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methoxy) phenyl]-N-[(1S)-1-(3-Methyl-1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine) according to any one of embodiments 1-3. .

Embodiment 5 The CRF₁ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4, 6-trimethylphenyl) pyrrole [3,2-e] pyrimidin-4-amine), or DMP904.

Embodiment 6 The method of any one of Embodiments 1 to 5, wherein the CRF₁ receptor antagonist is administered at bedtime.

Embodiment 7 The method of any one of Embodiments 1 to 6, wherein the CRF₁ receptor antagonist is administered during or prior to ACTH release by a predicted circadian rhythm.

Embodiment 8 The method of embodiment 7, wherein the CRF₁ receptor antagonist is administered 3-4 hours before ACTH release with a predicted circadian rhythm.

Embodiment 9 A method for reducing the levels of 17-OHP and ACTH in a subject having congenital adrenocortical hyperplasia (CAH) comprising: subjecting the subject to a CRF₁ receptor antagonist at bedtime Administering a step of administering.

Embodiment 10 The method of embodiment 9, wherein the CRF₁ receptor antagonist is administered during or prior to ACTH release by a predicted circadian rhythm.

Embodiment 11 The method of embodiment 9 or embodiment 10, wherein the CRF₁ receptor antagonist is administered 3-4 hours prior to ACTH release with a predicted circadian rhythm.

Embodiment 12 The CRF₁ receptor antagonist is compound I (NBI-77860; 2,5 dimethyl-3-[2-methyl-4-(methoxy) phenyl]-N-[(1S)-1-(3-Methyl-1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine) according to any one of embodiments 9-11. .

Embodiment 13 The CRF₁ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4, 6-trimethylphenyl) pyrrole [3,2-e] pyrimidin-4-amine), or DMP904.

A CRF₁ receptor antagonist for use in treating an embodiment 14 Congenital adrenal hyperplasia (CAH), wherein the CRF₁ receptor antagonist has a dissociation half-life greater than 30 minutes, CRF₁ receptors Antagonists.

Embodiment 15 wherein CRF₁ receptor antagonist has a dissociation half-life greater than 40 minutes, CRF₁ receptor antagonists described 14.

Embodiment 16 wherein CRF₁ receptor antagonist has a dissociation half-life greater than 50 minutes, CRF₁ receptor antagonist of embodiment 14.

Embodiment 17 The CRF₁ receptor antagonist is compound I (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methoxy) phenyl]-N-[[1(5)-1-(3 CRF according to any one of embodiments 14 to 16, which is -methyl-1,2,4-oxadiazol-5-yl] propyl] pyrazolo [1,5-a] pyrimidin-7-amine), CRF₁ receptor antagonist.

Embodiment 18 The CRF₁ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine), or OMP904 CRF₁ receptor antagonist according to any one of embodiments 14-16.

CRF₁ receptor antagonist of embodiment 19 wherein the CRF₁ receptor antagonists, which have any one of embodiments 14 to 18 suitable for administration at bedtime.

Embodiment 20 wherein CRF₁ receptor antagonists, CRF₁ receptor antagonist according to which has any one of embodiments 14-19 suitable for administration at the time of ACTH release by circadian rhythms predicted or before that.

Embodiment 21 wherein CRF₁ receptor antagonists, CRF₁ receptor antagonist according to which has any one of embodiments 14 to 20 suitable for administration to 3-4 hours prior to ACTH release by circadian rhythms predicted Antagonists.

In other embodiments, the methods and uses described above and herein provide the amount of glucocorticoid or mineralocorticoid to a full grown subject (eg. a human subject) with CAH. At least 10%, 15%, 20%, 30%, 40%, 50% from the recommended daily dose of GC to be administered (eg. hydrocortisone (HC), prednisone, prednisolone, dexamethasone, or fludrocortisone) And a step of reducing by 50%. In other embodiments, the methods and uses described above and herein provide that an amount of glucocorticoid or mineralocorticoid is administered to a growing subject (eg. a human subject) having CAH. Reducing at least 10%, 15%, 20%, 30%, 40%, 50%, 60% from the recommended daily dose of GC (eg. hydrocortisone) or mineral corticoid (eg. fludrocortisone) is further included.

These and other embodiments will be apparent upon reference to the following detailed description. To this end, various references describing in more detail certain background information, procedures, compounds and compositions are set forth herein, each of which is incorporated herein by reference in its entirety. Is done.

Terms not specifically defined herein are intended to be given the meanings given to them by those skilled in the art in view of the present disclosure and context. However, as used herein, unless specified to the contrary, the above terms have the meaning indicated. Throughout this specification, references to "one embodiment" or "an (one) embodiment" include at least one particular feature, structure, or characteristic described in connection with the above embodiment. Means. Thus, the appearances of the phrases "in one embodiment" or "in one (one) embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

Also, as used herein and in the appended claims, the singular forms "a", "one", "an", "the", "above", "this", "that" includes a reference to the plural unless the context clearly indicates otherwise. Thus, for example, reference to "a non-human animal" can refer to one or more non-human animals, or a plurality of such animals, and "a cell" Alternatively, reference to "the cell" includes reference to one or more cells and equivalents thereof (eg. a plurality of cells) known to those of skill in the art, and the like. If a method step is described or claimed and said steps are described to occur in a particular order, the second step "before" (ie, before) the second step occurs (or takes place) The description of the first step has the same meaning when the second step is rewritten to a state that occurs (or is performed) "following" the first step. The term "about" refers to a number or numerical range where the referenced number or numerical range is within experimental variability (or within statistical experimental error). It is an approximation, meaning that its number or numerical range can vary between 1% and 15% of the stated number or numerical range. Note also that the term "or (or)" is generally used in its sense including "and / or" (and / or) unless the context clearly indicates otherwise. Shall. The term "at least one" has the same meaning and understanding as the term "one or more", for example when referring to at least one compound or at least one composition.

FIG. 1 shows a schematic diagram of a steroid synthesis pathway in the adrenal gland. The most common form of CAH is caused by a 21-hydroxylase (also called 21- α -hydroxylase) deficiency, resulting in a decrease in cortisol and an increase in androgens (eg. testosterone and estrogens). A rarer type of classical CAH is 11 β -hydroxylase deficiency.

FIG. 2 presents a graph illustrating the effect of Compound I (NBI-77860) on ACTH levels in adrenalectomized rats. Rats were given orally 30 mg / kg Compound I (NBI-77860). Data are expressed as mean plasma concentration of ACTH ($\pm$ SEM).

FIGS. 3A-C represent graphs illustrating the effect of CRF₁ receptor antagonists on ACTH concentrations (distinguished by their dissociation half-life) in adrenalectomized rats.

FIG. 4 is a study design schematic of the clinical trial described in Example 6, designed to evaluate the safety, tolerability and plasma exposure of NBI-77860, and HPA (hypothalamic-pituitary-adrenal).) Represents the effect of this compound on endogenous levels of system hormones.

FIG. 5 represents mean 17-OHP (upper panel) and ACTH levels (lower panel) data during the 24 hour period after administration during the clinical study described in Example 6.

FIG. 6 depicts specific individual subject responses for 17-OHP (upper panel) and ACTH levels (lower panel) over time after administration of 300 mg and 600 mg of NBI-77860 and placebo.

(Detailed explanation)

As described herein, CRF₁ receptor antagonists were found to directly inhibit ACTH release in patients with CAH, thereby allowing normalization of androgen production. Administration of a CRF₁ receptor antagonist allows the use of lower and more physiological doses of hydrocortisone in subjects with CAH, thus reducing treatment-related side effects.

Newborn screening for CAH is performed by an immunoassay that measures 17-OHP levels in heelstick capillary blood specimens obtained within 72 hours of birth. The blood samples are analyzed for 17-OHP by a commercial dissociation enhanced lanthanide fluorescence immunoassay (DELFA; PerkinElmer, Waltham Massachusetts) (White et al., J. Pediatr. 163: 10-12 (2013)).

Nine states in the United States are using the second number of screening tests between 8 and 14 days after birth using biochemical and molecular genetic testing methods, with five more strongly Recommended. Such biochemical methods include immunoassay or liquid chromatography using organic solvent extracts followed by tandem mass spectrometry to determine the steroid ratio of 17-OHP, androstenedione, and 21-deoxycortisol to cortisol. (See, for example, Speiser et al., Int. J. Pediatr. Endocrinol. 2010: 494173, 2010). Genetic screening examines CYP21A2 mutations associated with CAH. Although not widely used in the United States, the addition of a second screen could potentially improve the sensitivity of the entire screening process (here, about 72% for the first screen alone).

Without newborn screening results, young girls with classic CAH are typically identified due to the presence of external genitals with ambiguous gender. Because men have normal external genitals when born, they are not diagnosed unless newborn screening is performed or other medical complications are noticed. Infants who are not initially diagnosed with CAH and experience the salt-losing form of the disease are later diagnosed in the context of insufficient weight gain, vomiting, hyperkalemia and hyponatremia within the first few weeks of life. The

Treatment of CAH is based on normalization of hormone and steroid levels using various drug therapies from diagnosis in childhood to adulthood. Glucocorticoids are currently the standard treatment in CAH and are used to both correct endogenous cortisol deficiency and reduce elevated pituitary ACTH levels (which drive increased androgen production) is done. Unlike the treatment of Addison's disease (decrease in adrenal function), where cortisol replacement is sufficient, treatment of CAH must also reduce ACTH production and control subsequent androgen excess. Thus, the goal of glucocorticoid treatment is to prevent cortisol supplementation and ACTH suppression in women to prevent masculinization and menstrual disturbances and to inhibit testicular adrenal rest tumor in men. Including. Mineralocorticoid supplementation is required to achieve normal plasma renin activity for maintenance of normal blood pressure, electrolyte balance, and volume state in those patients with a salt-lose form of CAH.

Glucocorticoid treatment regimens support normal physiology and also ensure that sufficient cortisol is available during events that can elicit strong stress responses (eg, comorbidities, exercise, hypotension). Must be secured. Careful monitoring is also necessary to avoid the occurrence of iatrogenic Cushing syndrome due to glucocorticoid overtreatment in an attempt to sufficiently suppress androgen production or Addison syndrome due to inadequate treatment. While overtreatment with mineralocorticoids can cause hypertension, inadequate treatment can lead to hypotension, salt loss, fatigue and increased demand for glucocorticoids. Typical laboratory tests to monitor the efficacy of treatment include measurement of 17-OHP, androstenedione, testosterone, renin activity, and electrolyte plasma concentrations.

Adult patients with CAH have an increased prevalence of cardiovascular risk factors including obesity, hypertension, and insulin resistance (eg, Kim et al., *Semin Reprod. Med.* 27 (4): 316-21 (2009)). From a large cohort study of pediatric and adult CAH patients (n = 244), patients frequently experience inadequate hormonal control and the aforementioned adverse outcomes despite being prescribed various glucocorticoid treatment regimens. (See, for example, Feinstein et al., *J. Clin. Endocrinol. Metab.* 97 (12): 4429-38 (2012)).

Treatment of CAH involves glucocorticoids (usually hydrocortisone in children but often more potent drugs with a narrow therapeutic index, such as dexamethasone in adults), and mineralocorticoids (if needed for salt loss). This includes attempts to normalize cortisol deficiency (usually fludrocortisone). However, the glucocorticoid dose required to achieve sufficient suppression of excess androgens is usually sufficient for normal physiological doses used only for cortisol replacement, as in patients with Addison's disease. It has exceeded. This increased exposure to glucocorticoids can result in iatrogenic Cushing syndrome, increased cardiovascular risk factors, impaired glucose tolerance, and decreased bone mineral density in CAH patients (eg, Elnefave et al. M., *J. Pediatr. Endocrinol. Metab.* 21: 1155-62 (2008); King et al., *J. Clin. Endocrinol. Metab.* 91 (3): 856-59 (2006); Migeon et al. *Metab. Clin. North Am.* 30: 193-206 (2001)).

Adrenocorticotrophic hormone releasing factor (CRF) was isolated from sheep hypothalamus and identified as a 41 amino acid peptide. CRF has been found to produce significant changes in the functions of the endocrine system, nervous system, and immune system. CRF is the main physiological of basal and stress-induced release of adrenocorticotrophic hormone ("ACTH"), β -endorphin, and other proopiomelanocortins ("POMC") (anterior pituitary derived peptides). It is thought to be a regulator (see, eg, Vale et al., *Science* 213: 1394-1397, 1981). Secretion of CRF causes ACTH release from corticotrophs in the anterior pituitary gland through binding to the CRF₁ receptor, a member of the class B family of G protein coupled receptors.

Due to the physiological importance of CRF, the development of biologically active small molecules that have significant CRF₁ receptor binding activity and can antagonize the CRF₁ receptor is still a desired goal, anxiety, it continues to be the subject of ongoing research and development for the treatment of depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse.

The pituitary hormone ACTH is under the control of the hypothalamic corticotropin releasing factor (CRF) and stimulates cholesterol uptake and drives the synthesis of pregnenolone that initiates steroidogenesis in the adrenal gland (see FIG. 1). about). The adrenal cortex is composed of three zones, which produce distinct classes of hormones, many of which are driven by ACTH, which mobilizes cholesterol through this pathway. Loss of these enzymes as a result of mutation or deletion causes an increase in substrate concentration. The most common form of CAH resulting from mutations or deletions in the 21-hydroxylase gene (CYP21A2) is a potent androgen due to the accumulation of the steroid precursors progesterone and 17-hydroxyprogesterone (17-OHP). is produced by the adrenal glands. Plasma levels of 17-OHP can reach 10 to 1000 times the normal concentration in these cases. These increases result in overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone, causing masculinization in women. Furthermore, 21-hydroxylase deficiency in CAH causes inadequate biosynthesis of glucocorticoids and mineralocorticoids, specifically cortisol and aldosterone. Cortisol is an important negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates inhibition on the hypothalamus and pituitary gland, which increases ACTH levels. Excessive ACTH stimulation causes cord and reticulum hypertrophy, resulting in adrenal hyperplasia.

In one embodiment, the CRF₁ receptor antagonist useful for the treatment of CAH is NBI-77860, 2,5-dimethyl-3-[2-methyl-4-(methoxy) phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl) propyl] pyrazolo [1,5-a] pyrimidin-7-amine (also referred to herein as "Compound I") This has the following structure:

Compound I is a potent CRF₁ antagonist with binding pK_i = 8.2 (eg Tellew et al., *Bioorg. Med. Chem. Lett.* 20: 7259, 2010 and International Patent Application Publication No. WO 2006/044958). (Both of which are incorporated herein by reference in their entirety). As described herein, Compound I has a potent ACTH-lowering effect as shown in adrenalectomized rats.

In another embodiment, CRF₁ receptor antagonists useful for treating CAH are US Pat. Nos. 6,586,456, 6,806,282, 6,531,475, 6,64,261, 6,610,678, WO 98/08846, WO 98/11075, WO 99/10350, WO 2000/059888, WO 2006/044821, WO 2006/102194, WO 2006/107784, WO 2006/116412, WO 2006/126718, WO 2007/066955, WO 2007/069671, WO 2008/036541, WO 2008/036579, WO 2008/051533, WO 2008/082003, WO 2008/083070, WO 200 / 136377, WO 2009/008552, WO 2009/144632, WO 2010/014289, WO 2010/014687, WO 2010/015628, WO 2010/015655, WO 2010/062718, WO 2010/096426, WO 2011/043387, WO 2011 / 092293, WO 2011/095450, WO 2011/092293, and WO 2011/043381.

In yet another embodiment, the CRF₁ receptor antagonist is NBI-30775, CP-316, 311, Fexasetfonto, emicerfont, SSR-125543 [4-(2-Chloro-4-methoxy-5-methylphenyl)-1-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl) ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine], SSR-126374, ONO-2333, NBI-34041, JNJ-195567470, GSK536529, PF-00572778, CP-376395, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2, 4,6-trimethylphenyl) pyrrolo [3,2-e] pyrimidine-4-amine), and DMP904.

In yet another embodiment, the CRF₁ receptor antagonist has a dissociation half-life (t_{1/2}) greater than 30 minutes, and in another embodiment greater than 40 minutes, and in another embodiment greater than 50 minutes. Have. The dissociation half-life of a particular CRF₁ receptor antagonist is determined by the technique disclosed in Example 3. Representative CRF₁ receptor antagonists of these embodiments include Compound I, NBI-30775, NBI-34041, SSR-125543A, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2, 4,6-trimethylphenyl) pyrrolo [3,2-e] pyrimidin-4-amine), and DMP904.

With respect to the compounds described herein, it is also to be understood that when a particular position is designated as hydrogen, such hydrogen (H) can be replaced with deuterium (D). Incorporation of deuterium instead of hydrogen is known to produce significant effects on the physiological and pharmacological activity of the substituted compound. To this end, it should be understood that deuterium substitution of hydrogen means that the deuterium abundance at that position is substantially greater than the natural deuterium abundance. Thus, in one embodiment, representative compounds include the following.

In another embodiment, any of the aforementioned compounds may incorporate a stable or radioactive isotope. Thus, the use of isotopically-labelled compounds identical to those described herein is also contemplated, wherein one or more atoms are atoms that differ from some atomic mass or mass number normally found in nature. Substituted by an atom having a mass or mass number. Examples of isotopes that can be incorporated into these compounds include hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine isotopes, eg. deuterium (^2H) as discussed above, and ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl are included, but are not limited thereto. Certain isotopically-labelled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are also useful in drug or substrate tissue distribution assays. Tritium hydrogen (^3H) and carbon ^{14}C (^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Substitution with heavier isotopes (eg. deuterium (^2H)) may provide certain metabolic benefits resulting from greater metabolic stability, eg. increased in vivo half-life or reduced dose requirements. Therefore, it may be preferable in some environments. Isotopically labeled compounds can generally be prepared by performing procedures routinely practiced in the art. (Effect on plasma ACTH in adrenalectomized rats)

Adrenalectomy eliminates circulating corticosterone (the main glucocorticoid) in rats and eliminates negative feedback control of the HPA system at both the hypothalamic and pituitary (adrenocortical hormone producing cells) levels, and thus plasma ACTH (See, for example, Mims et al., J. Natl. Med. Assoc. 69: 145-47 (1977)). Intravenous injection of peptide CRF $_1$ receptor antagonists has been shown to reduce high plasma ACTH levels in adrenalectomized (ADX) rats (see, eg. Rivier et al., J. Med. Chem. 12: 42: 3175). These findings were reproduced with the low molecular weight NBI-77860 (Compound I). In adrenalectomized rats, Compound I has a potent capacity for ACTH reduction. The greatest reduction in ACTH correlated with the peak plasma concentration of NBI-77860, however, the duration of the ACTH-lowering effect was beyond drug plasma exposure. Thus, there is a predictable relationship between integrated plasma exposure of NBI-77860 and in vivo efficacy after oral administration in adrenalectomized rats.

The effectiveness of a compound as a CRF receptor antagonist can be determined by various assays. The CRF antagonists described herein can inhibit the specific binding of CRF to its receptor and, as a result, can antagonize the activity associated with CRF. A compound can be evaluated for activity as a CRF antagonist by one or more commonly accepted assays, including the assays described in the Examples. CRF antagonists useful in the methods described herein include compounds that exhibit affinity for the CRF receptor.

While not wishing to be bound by theory, in the treatment of CAH, CRF receptor antagonists potentially block ACTH release from pituitary corticotrophic cells, thereby reducing androgen production. Allows for a more sophisticated treatment methodology for cortisol supplementation. Animal and human studies have shown the pharmacological effect of Compound I (NBI-77860) on ACTH release. Standard biomarker assessments used by endocrinologists when monitoring treatment efficacy can be used to monitor the effects of this CRF $_1$ receptor antagonist. Plasma levels of 17-OHP, androstenedione, testosterone, cortisol and ACTH, and urinary metabolites of these steroids are easily measured in both children and adults, giving quick and meaningful data regarding the effects of treatment. (Pharmaceutical compositions and methods for treatment)

The present disclosure relates to a pharmaceutical composition for use in a method for treating CAH comprising any one of the CRF antagonist compounds described herein and a pharmaceutically acceptable excipient. Provide further. Pharmaceutically acceptable excipients are physiologically and pharmaceutically suitable, non-toxic and inert substances or components that do not interfere with the activity of the active ingredient; it can be said. The CRF antagonist compound is used in a pharmaceutical composition for use in a treatment or preventive (or prophylactic) treatment (eg. reducing exacerbation of CAH disease or the occurrence or recurrence of one or more symptoms of the disease). It can be formulated. The methods and excipients described herein are exemplary and are in no way limiting. Pharmaceutically acceptable excipients are well known in the pharmaceutical art and are described, for example, by Rowe et al., Handbook of Pharmaceutical Excipients: A Comprehensive Guide to Uses, Properties, and Safety, 5th Ed., 2006 and Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)). Examples of pharmaceutically acceptable excipients include sterile saline and phosphate buffered saline at physiological pH. Preservatives, stabilizers, dyes, buffering agents and the like may be provided in the pharmaceutical compositions. In addition, antioxidants and suspending agents can also be used.

Therapeutic and / or prophylactic benefits include, for example, improved clinical outcome (both therapeutic treatment and prophylactic or preventative measures), where the objective is to reduce undesirable physiological changes or disorders. Preventing, delaying or delaying (reducing), or preventing or delaying or delaying (reducing) the spread or severity of such disorders. As discussed herein, beneficial or desirable clinical results from treating a subject include, but are not limited to: Does it result from a disease, condition or disorder to be treated? Or a reduction, reduction, or alleviation of symptoms associated with them; a decrease in the occurrence of symptoms; an improvement in quality of life; a condition that is free of disease (ie. subject has symptoms (based on which the disease is diagnosed) Decrease the likelihood or tendency to show); decrease the degree of disease; stable (ie. not aggravating) disease; delay or delay in disease progression; improvement or reduction of the disease state As well as detectable or undetectable, regression (whether partial or whole); and / or overall survival. "Treatment" can also mean prolonging survival as compared to expected survival if the subject does not receive treatment. Subjects in need of treatment include those who already have the condition or disorder, as well as subjects who are prone to or at risk of developing the disease, condition or disorder, and the disease or condition. Or people whose disability should be prevented (ie. reducing the likelihood of the disease, disorder or condition occurring). The subject can be a human or non-human mammal (eg. rat, mouse, dog, cat, farm animal, zoo animal).

Optimal dosages can generally be determined using experimental models and / or clinical trials. The optimal dose can depend on the subject's body mass, weight, or blood volume. In general, the amount of a compound described herein present in a dose ranges from about 0.1 mg to about 30 mg / kg subject body weight. In certain embodiments, the single dose is about 50-1000 mg. The use of the minimum dose that is sufficient to provide effective treatment is usually preferred. Subjects can generally be monitored for therapeutic efficacy by clinical assessment and using assays suitable for the condition being treated or prevented. This assay is familiar to those skilled in the art and is described herein. The level of the compound administered to the subject is other biologicals in the biological fluid, eg. blood, blood fraction (eg. serum) and / or urine, and / or derived from the subject. Can be monitored by determining the level of the compound in a laboratory sample. Any method practiced in the art to detect the compound can be used to measure the level of the compound during the course of a treatment regimen.

The dose of the composition for treating CAH or related diseases or disorders comprising at least one of the compounds described herein depends on the condition of the subject, ie the stage of the disease, the disease. The severity of symptoms caused, general health, and age, gender and weight, and other factors apparent to those skilled in the medical arts. Similarly, the dose of the compound can be determined according to parameters understood by those skilled in the medical arts.

The pharmaceutical compositions described herein comprising at least one of the CRF $_1$ antagonist compounds described herein are among several routes that efficiently deliver an effective amount of the compound. Any one can be administered to a subject in need. Such administration routes include, for example, oral, parenteral, intestinal, rectal, nasal, buccal, sublingual, intramuscular, and transdermal. Compositions administered by these routes of administration and the like are described in more detail herein.

Administration of the disclosed compounds or compositions includes night administration or administration prior to going to bed (ie, bedtime administration). As used herein, bedtime administration is clinically relevant to the CRF₁ antagonist at or before (eg, 2 to 5 hours before) the release of ACTH according to the expected circadian rhythm. Administration that is intended to deliver a concentration. This ACTH release is typically 1-2 am, and most orally administered drugs have a T_{max} of several hours, so, for example, 3 to 3 of ACTH release due to the expected circadian rhythm. Administration at 10pm, 4 hours before, is desirable. This same prepulse bedtime administration may be adapted for shift workers (eg, people who work at night and sleep during the day), in which case the administration may not necessarily occur at night. Thus, administration depends on the expected circadian rhythm of ACTH release and can vary depending on the individuals (ie, subject, patient's) specific work and sleep patterns. In certain embodiments, the CRF₁ receptor antagonists described herein (eg, NBI-77860, or NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalanine (N-butyl-N-Ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl) pyrimido [3,2-e] pyrimidin-4-amine), or any one of DMP904) Administered about 2 to 5 hours before (ie, first) the ACTH release due to circadian rhythm. In other embodiments, the CRF₁ receptor antagonist is administered to the subject during about 2-4 hours or 3-5 hours prior to ACTH release with the expected circadian rhythm. In a more specific embodiment, the CRF₁ receptor antagonist is administered to the subject during about 3-4 hours prior to the release of ACTH according to the expected circadian rhythm.

Also provided herein are methods for reducing 17-OHP and / or ACTH levels in a subject with CAH (ie, patient, individual) by administering a CRF₁ receptor antagonist. In certain embodiments, the antagonist is administered at or prior to ACTH release with an expected circadian rhythm. In certain other embodiments, the CRF₁ receptor antagonist is administered during about 2-4 hours or about 3-5 hours prior to the expected circadian rhythm ACTH release. In a more specific embodiment, the CRF₁ receptor antagonist is administered to the subject during about 3-4 hours prior to ACTH release with the expected circadian rhythm.

Described herein including administering to a female subject in need a CRF₁ receptor antagonist in the manner described herein that causes a decrease in the levels of ACTH and 17-OHP in said subject. Methods can result in reduced release of androgens (eg, testosterone and androstenedione). The dose of glucocorticoid can be concomitantly reduced by a clinically significant amount, which in turn reduces side effects. Produce.

The amount of glucocorticoid (GC) and mineralocorticoid (MC) for maintenance therapy in patients with CAH and young growing patients and for maintenance therapy in mature patients is known to those skilled in the art. For example, guidelines can be found in Speiser et al. (J. Clin. Endocrinol. Metab. 95: 4133-60 (2010) (incorporated by reference in its entirety) and shown in Tables 1 and 2 therein, in particular, young growth with CAH. With respect to patients in the art, those skilled in the art will recognize that administration too high with GC can interfere with stature growth in the patient, and thus a goal for treating patients with CRF₁ receptor antagonists. The methods described herein can include reducing the dose of GC in a clinically significant manner.

In certain embodiments, the method for treating CAH by administering a CRF₁ receptor antagonist administers GC at a dose lower than the currently recommended GC dose for treating a subject with CAH. A step can be further included. If the subject is a mature patient, the GC dose (eg, hydrocortisone (HC), prednisone, prednisolone, dexamethasone, or fludrocortisone recommended for maintenance therapy in mature subjects) is: 15-25 mg / day HC; 5-7.5 mg / day Prednisone, 4-6 mg / day Prednisolone, 0.25-0.5 mg / day Dexamethasone, or 0.05-0.2 mg / day Fludrocortisone. The dose can be reduced to the extent of about 10%, 15%, 20%, 30%, 40%, 50%, 60% or more. In growing subjects with CAH, the recommended dose of GC (eg, HC) can be reduced from a total recommended dose of 10-15 mg / m² / day and / or 0.05-0.2 mg. The total dose of fludrocortisone / day is about 10%, 15%, 20%, 30%, 40%, 50%, respectively, in subjects receiving a CRF₁ receptor antagonist as described herein. It can be reduced by as much as 50% or more. In one embodiment, a method described herein comprising administering an effective amount of a CRF₁ antagonist to a subject in need comprises a clinically significant reduction in ACTH levels compared to placebo. Produce. In a specific embodiment, administering an effective amount of a CRF₁ antagonist to a subject in need results in a clinically significant reduction in ACTH levels compared to placebo, wherein the reduction is at least 25%. In another embodiment, administering an effective amount of a CRF₁ antagonist to a subject in need results in a clinically significant decrease in ACTH levels compared to placebo, wherein the decrease is at least 50%. For guidelines on the administration of glucocorticoids and mineralocorticoids, see Speiser et al. See (above).

In another embodiment, a method described herein comprising administering an effective amount of a CRF₁ antagonist to a subject in need comprises a 17-OHP level clinically compared to a placebo. A significant decrease occurs. In another specific embodiment, administering an effective amount of a CRF₁ antagonist to a subject in need results in a clinically significant decrease in 17-OHP levels compared to placebo, wherein The decrease is at least 25%. In yet another embodiment, administering an effective amount of a CRF₁ antagonist to a subject in need results in a clinically significant reduction in 17-OHP levels compared to placebo, wherein the reduction is at least 50%.

In one embodiment, a method described herein comprising administering an effective amount of a CRF₁ antagonist to a subject in need comprises both ACTH and 17-OHP levels compared to placebo. Produces a clinically significant decrease in In certain embodiments, administering an effective amount of a CRF₁ antagonist to a subject in need results in a clinically significant decrease in both ACTH and 17-OHP levels compared to placebo. Where the reduction is at least 25%. In another specific embodiment, administering an effective amount of a CRF₁ antagonist to a subject in need results in a clinically significant decrease in both ACTH and 17-OHP levels compared to placebo. Occurs, where the reduction is at least 50%.

The pharmaceutical composition can be in the form of a solution. Alternatively, they can be in the form of a solid (eg, powder, tablet, etc.). A composition comprising any one of the compounds described herein can be formulated for sustained or slow release. Such compositions can generally be prepared using well-known techniques and can be administered, for example, by oral, rectal or subcutaneous implantation, or by implantation at the desired target site. The sustained release formulation may comprise a compound dispersed in a carrier matrix and / or contained within a reservoir surrounded by a rate controlling membrane. Excipients for use within such formulations may be biocompatible and biodegradable; preferably, the formulation provides a relatively constant level of active ingredient release. The amount of active compound contained within the sustained release formulation will depend on the site of implantation, the rate of release and the expected duration, and the nature of the condition to be treated or prevented.

For oral formulations, at least one of the compounds described herein can be used alone or in combination with appropriate additives, eg, conventional additives (eg, lactose, mannitol, Corn starch or potato starch); with binders; with disintegrants; with lubricants; and, if desired, with diluents, buffering agents, wetting agents, preservatives, colorants and flavoring agents, tablets, Powders, granules or capsules can be made. The compounds can be formulated with buffering agents and / or enteric coatings to provide protection of the compounds from the low pH of the stomach environment. The compounds included in the composition can be formulated for oral delivery, for example, with a flavoring agent in a liquid, solid or semi-solid formulation and / or with an enteric coating. Oral formulations can be provided as gelatin capsules that can contain the active compound together with a powdered carrier such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar carriers and diluents can be used to make compressed tablets.

Example 1: CRF receptor binding activity CRF antagonists as used in the methods described herein are described in Grigoriadis et al. (See, eg, Mol. Pharmacol vol 50, pp 679-686, 1996) and Hoare et al. (See, eg, Mol. Pharmacol 63: 751-765, 2003) and can be assessed for binding activity to the CRF receptor by a standard radioligand binding assay as generally described. By utilizing a radiolabeled CRF ligand, the assay can be used to assess the binding activity of the compounds described herein with any CRF receptor subtype.

Briefly, the binding assay involves replacing a radiolabeled CRF ligand with the CRF receptor. More specifically, the binding assay is performed in 96-well assay plates using 1-10 µg cell membranes derived from cells stably transfected with human CRF receptor. Each well contains a compound of interest or a reference ligand (eg, sorbazine, urocortin I, or CRF), 0.05 mL of [¹²⁵I] tyrosine-sorbazine (final concentration about 150 pM or as determined by Scatchard analysis), K_D and about 0.05 mL assay buffer (eg Dulbecco's phosphate buffered saline, 10 mM magnesium hydrochloride, 2 mM EGTA) containing 0.1 mL cell membrane suspension containing the CRF receptor. The mixture is incubated for 2 hours at 22 ° C., followed by separation of bound and free radioligand by rapid filtration through glass fiber filters. After three washes, the filter is dried and the radioactivity (¹²⁵ I Auger electrons) is counted using a scintillation counter. All radioligand binding data can be analyzed using the nonlinear least square curve fitting program Prism (GraphPad Software Inc) or XLfit (ID Business Solutions Ltd).

Example 2: CRF₁ receptor agonist activity

Fleck et al. (As previously reported in J. Pharmacology and Experimental Therapeutics, 341 (2): 518-531, 2012) (hereinafter referred to as "Fleck et al.", incorporated herein by reference in its entirety). Activity of the produced CRF₁ receptor antagonists. Such activity is reported as a kinetically derived affinity (K_i) calculated from the association rate constant (k₁) and dissociation rate constant (k₋₁) by the following equation:

$$K_i = k_{-1} / k_1$$

See also Fleck et al. in As reported, kinetic K_i of the CRF₁ receptor antagonist listed in Table 1 below were reported:

By this same technique, the kinetic K_i of compound I (NBI-77860) was found to be as follows:

Example 3: Dissociation half-life of the CRF₁ receptor antagonist (t_{1/2})

The dissociation half-life (t_{1/2}) of a CRF₁ receptor antagonist as used in the methods described herein is determined by the method of Fleck et al. It is evaluated by the technique described in. As described therein, the dissociation rate constant for labeled and unlabeled ligands is expressed as k₋₁ while the drug dissociation half-life of the receptor (t_{1/2}) (this is equal to the median residence time) is calculated from the dissociation rate constant (k₋₁) by the following equation:

$$t_{1/2} = 0.693 / k_{-1}$$

Fleck et al. As reported in, the dissociation half-life (t_{1/2}) of the CRF₁ receptor antagonists listed in Table 2 below was reported.

By this same technique, the dissociation half-life of Compound I (NBI-77860) was found to be as follows:

Thus, CRF₁ receptor antagonists having a dissociation half-life (t_{1/2}) of greater than 30 minutes include antalarmin, NBI-34041, DMP904, NBI-30775, SSR125543A, and NBI-77860 (Compound I) (But is not limited to these). These same compounds also are representative of the CRF₁ receptor antagonist having a dissociation half-life greater than 40 minutes (t_{1/2}) and dissociation half-life greater than 50 minutes to (t_{1/2}).

Example 4: Reduction of ACTH in adrenalectomized rats

Compound I (NBI-77860) (see, for example, Tellaw et al., Bioorg. Med. Chem. Lett. 2019, 20: 7259; see WO2006044958) binds pK_i 8.2, kinetic K_i 49nM (above, Table 1) and dissociated t_{1/2} 58 min (Table 2 above) are potent CRF₁ antagonists.

Intravenous injection of peptide CRF₁ receptor antagonists has been shown to reduce high plasma ACTH levels in adrenalectomized (ADX) rats (eg, Rivier et al., J. Med. Chem. 12: 42: 3175). 82 (1999)). These findings were reproduced with the low molecular weight NBI-77860. When administered orally to ADX rats (n = 6 / group), a 30 mg / kg single dose of NBI-77860 significantly reduced plasma ACTH levels for up to 5 hours (see FIG. 2). The duration of efficacy correlated with the peak plasma concentration over time over drug plasma exposure. There is a predictable relationship between NBI-77860 integrated plasma exposure and in vivo efficacy after oral administration in adrenalectomized rats

Fleck et al. Also report the effects of CRF₁ receptor antagonists, distinguished by their dissociation half-life on plasma ACTH levels in adrenalectomized rats; ie, NBI 30775, NBI 34041 and NBI 35965. At the highest dose (10 mg / kg), all three ligands drastically reduced ACTH (1 hour after injection, FIGS. 3A-C). After a longer duration, a clear difference emerged between NBI 35965 and the other two ligands. The ACTH level returned to vehicle level by 2 hours for NBI 35965 (FIG. 3C), whereas the response persisted for 4-6 hours for NBI 30775 and NBI 34041 (FIG. 3A). And FIG. 3B).

Example 5: Pharmacodynamic effect of Compound I in humans

In this study, the pharmacodynamic effects of NBI-77860 (Compound I) on human subjects were compared with placebo and a single dose of alprazolam (0.75 mg) by the HPA system produced by metyrapone (0.04 g / kg). Evaluated by observing the effect of a single oral dose on response. Metyrapone blocks cortisol synthesis in the adrenal gland (thus mimicking the cortisol deficiency of CAH) and is associated with a sharp increase in ACTH levels.

Primary analysis was performed by determining ACTH values (AUC (30 minutes to 4 hours)) between 30 minutes and 4 hours after administration. In this analysis, the following observations were made compared to placebo. A significant reduction in ACTH AUC (30 minutes to 4 hours) was observed with alprazolam and NBI-77860, 400 mg treatment. A non-significant decrease in ACTH AUC (30 minutes to 4 hours) was observed with NBI-77860, 50 mg treatment. An increase in AUC (30 minutes to 4 hours) was observed with NBI-77860, 10 mg treatment.

The analysis performed on ACTH values (AUC (2-4 hours)) between 2 and 4 hours post-dose (period when exposure reached C_{max} values) compared to the placebo treatment period. NBI-77860, 400 mg and 50 mg, the ACTH level was significantly reduced during the treatment period; however, the reduction was not observed at the 10 mg dose of NBI-77860.

Example 6: Clinical study

In this study, NBI-77860 (Compound I) was administered with the title "Phase 1, single-blind, placebo-controlled fixation to evaluate the safety and tolerability of NBI-77860 in adult women with congenital adrenocortical hyperplasia. Evaluated in a clinical study called "Phase 1, Single-Blind, Placebo-Controlled, Fixed Sequence, Single-Dose Study" (IND 117,388). The study was a single-blind, placebo-controlled, single-center, fixed-order, single-dose clinical trial in adult female classic CAH patients. This was designed to evaluate the safety, tolerance, and plasma exposure of NBI-77860, and the effect of this compound on endogenous levels of HPA hormones.

A total of 8 female subjects (aged 19-58 years) medically diagnosed with classic 21-hydroxylase deficient CAH received NBI-77860 300 mg, 600 mg, and 3 different treatment periods. A single bedtime dose (hs) of placebo was administered (see study design schematic in FIG. 4). The subject's usual morning dose of concurrent steroid treatment was delayed until a 16 hour blood sample was collected (ie, up to about 1400 hours).

The PD endpoint for this study is the HPA biomarker of interest in this patient population; namely, 17-hydroxyprogesterone (17-OHP; as the primary PD endpoint), adrenocorticotrophic hormone (ACTH), androstenedione, Testosterone and serum cortisol levels were included. The initial analysis of PD variables was a survey of

grouped subject data for each biomarker (mean% from pre-dose levels for the two active dosing conditions compared to placebo conditions) Expressed as a change). Data for average 17-OHP and ACTH levels over the 24 hour period after administration is provided in FIG.

A consistent and clinically significant decrease from pre-dose levels of both 17-OHP and ACTH was observed in these CAH patients throughout the post-dose period after administration of NBI-77860 compared to placebo. In addition to group mean data, individual responses were assessed and treatment "responders" were at least 50 in 17-OHP and ACTH under active NBI-77860 compared to placebo during the morning peak period. Conservatively defined as those subjects with% reduction. This responder analysis resulted in a fairly large responder rate of 50% in the study (none of these patients were responders during the first placebo treatment period). Furthermore, the 300 mg dose produced the same effects on 17-OHP and ACTH as the 600 mg dose. Examples of individual subject responses for these biomarkers are provided in FIG.

The various embodiments described above can be combined to provide further embodiments. All U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications mentioned in this specification and / or listed in the application data sheet are U.S. provisional patent applications, 61,929,941 (filed January 21, 2014); 61,981,033 (filed April 17, 2014); and 62 / 069,155 (October 27, 2014) All of which are hereby incorporated by reference herein. Aspects of the above embodiments can be modified to provide still further embodiments if necessary to use the various patents, applications, and published concepts.

These and other changes can be made to the above embodiments in light of the above detailed description. In general, in the following claims, the terminology used shall be construed to limit the scope of the claims to the specific embodiments disclosed in the specification and the claims. Rather, it is intended to be construed to include all possible embodiments, along with the full scope of equivalents (to which such claims are entitled). Accordingly, the claims are not limited by the above disclosure

Patent Citations (57)

Publication number	Priority date	Publication date	Assignee	Title
JP2010304344A *	2006-09-20	2010-02-12	イーライ リリー アンド カンパニー	Thiazolepyrazolopyrimidines as CRF1 receptor antagonists
Family To Family Citations				
JP34949582B1	1969-01-20	1974-12-27		
FR2692893B1	1992-06-24	1994-09-02	Sanofi Elf	Branched alkylamino thiazole derivatives, processes for their preparation and pharmaceutical compositions containing them.
US5664261B2	1996-02-07	2003-12-16	Neurocrine Biosciences, Inc.	Pyrazolopyrimidines as CRF receptor antagonists
TW477787E	1996-08-27	2002-03-01	Pfizer	Pyrido six-membered nitrogen-containing cyclic ring derivatives having corticotropin releasing factor antagonist activity and pharmaceutical composition containing same
EP0927171B1	1996-09-16	2002-02-20	Du Pont Pharmaceuticals Company	Pyrazinones and triazinones and their derivatives thereof
AU7644693A	1997-04-22	1998-11-13	Janssen Pharmaceutica N.V.	Crf antagonistic quino- and quinazolines
EP0937081A1	1997-08-22	1999-08-25	Du Pont Pharmaceuticals Company	NITROGEN SUBSTITUTED IMIDAZO 4,5-C]PYRAZOLES AS CORTICOTROPIN RELEASING HORMONE ANTAGONISTS
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FR2796808B3	1999-07-15	2001-08-17	Sanofi Synthelabo	NOVEL AMINOTHIAZOL DERIVATIVES, THEIR PREPARATION AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING THEM
FR2802530B1	1999-12-17	2002-02-22	Sanofi Synthelabo	NOVEL BRANCHED SUBSTITUTED AMINO DERIVATIVES OF 3-AMINO-1-PHENYL-1H [1,2,4] TRIAZOLE, METHODS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM
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CA2556160A1	2004-02-13	2005-09-01	Pfizer Products Inc.	Therapeutic combinations of atypical antipsychotics with corticotropin releasing factor antagonists
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TW370820B	2005-04-27	2012-08-21	Takeda Pharmaceutical	Fused heterocyclic compounds
US20090234117A1	2005-05-27	2009-09-17	Toshihiko Kashiwagi	Pyrazolopyrimidine Derivative

G8051995700	2005-09-30	2005-11-09	Sb Pharmco Inc	Chemical compound
WO2005054719A2	2005-11-10	2007-05-18	Topotarget UK Limited	Histone deacetylase (hdac) inhibitors (pxd101) for the treatment of cancer alone or in combination with chemotherapeutic agent
EP1961745A1	2005-12-12	2008-08-27	Ono Pharmaceutical Co., Ltd.	Bicyclic heterocyclic compound
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WO2008083070A1	2006-12-29	2008-07-10	Neurogen Corporation	Crf1 receptor ligands comprising fused bicyclic heteroaryl moieties
TW200902019A	2007-04-26	2009-01-16	Ono Pharmaceutical Co	Dicyclic heterocyclic compound
WO2009008552A1	2007-07-11	2009-01-15	Taisho Pharmaceutical Co., Ltd.	8-aryl-4-alkylpyrrolo[2,3,4-de]quinolin-5(4h)-one and 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-de]quinolin-5-ol derivatives
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US7932256B2	2008-07-31	2011-04-26	Bristol-Myers Squibb Company	(S)-4-(1-cyclopropyl-2-methoxyethyl)-6-(6-(difluoromethoxy)-2,5-dimethylpyridin-3-ylamino)-5-oxo-4,5-dihydropyrazine-2-carbonitrile; a pyrazinone modulator of corticotropin-releasing factor receptor activity
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US8273900B2	2008-08-07	2012-09-25	Novartis Ag	Organic compounds
CN102245117B	2008-11-03	2014-04-16	斯恩蒂斯有限公司	Adjustable rod assembly
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EP3548035A4	2016-11-30	2020-07-22	Case Western Reserve University	Combinations of 15-pgdh inhibitors with corticosteroids and/or tnfr inhibitors and uses thereof
WO201821988A1	2017-06-02	2018-12-06	Bayer Pharma Aktiengesellschaft	Self-microemulsifying drug delivery systems
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JP2022508317A	2018-12-07	2022-01-19	ニューロクライン バイオサイエンス ズ、インコーポレイテッド	CRF1 receptor antagonist for treating congenital adrenal hyperplasia, its pharmaceutical formulation and solid form

* Cited by examiner, † Cited by third party

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JP2020539831A *	2017-09-14	2020-10-29	スプリューズ バイオサイエンス イン コーポレイテッド	Corticotropin-releasing factor receptor antagonist
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KR20220052927A *	2019-07-19	2022-04-28	스프루스 바이오텍스(주)	How to treat congenital adrenal hyperplasia
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* Cited by examiner, † Cited by third party, § Family to family citation

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Kirkgoz et al.	2018	Primary adrenal insufficiency in children: Diagnosis and management
EP1885695A1	2008-02-13	Pharmaceutical combination of an aldosterone synthase inhibitor and a glucocorticoid receptor antagonist or a cortisol synthesis inhibitor or a corticotropin releasing factor antagonist
Basta Kaim et al.	2011	Hyperactivity of the hypothalamus-pituitary-adrenal axis in lipopolysaccharide-induced neurodevelopmental model of schizophrenia in rats: effects of antipsychotic drugs
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CA2446506C	2012-04-10	Methods for treating delirium using glucocorticoid receptor-specific antagonists
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Priority And Related Applications

Child Applications (1)

Application	Priority date	Filing date	Relation	Title
JP2019043466A	2014-01-21	2019-03-11	Division	CRF1 receptor antagonist for the treatment of congenital adrenal hyperplasia

Priority Applications (7)

Application	Priority date	Filing date	Title
US201461929941P	2014-01-21	2014-01-21	US Provisional Application
US61/929,941		2014-01-21	
US201461981033P	2014-04-17	2014-04-17	US Provisional Application
US61/981,033		2014-04-17	
US201462069155P	2014-10-27	2014-10-27	US Provisional Application
US62/069,155		2014-10-27	
PCT/US2015/012315	2014-01-21	2015-01-21	Crfl receptor antagonists for the treatment of congenital adrenal hyperplasia

Applications Claiming Priority (1)

Application	Filing date	Title
JP2019043466A	2019-03-11	CRF1 receptor antagonist for the treatment of congenital adrenal hyperplasia

Legal Events

Date	Code	Title	Description
2018-01-19	A521	Request for written amendment filed	Free format text: JAPANESE INTERMEDIATE CODE: A523 Effective date: 20180119
2018-01-19	A621	Written request for application examination	Free format text: JAPANESE INTERMEDIATE CODE: A621 Effective date: 20180119
2018-12-11	A131	Notification of reasons for refusal	Free format text: JAPANESE INTERMEDIATE CODE: A131 Effective date: 20181211
2019-03-11	A521	Request for written amendment filed	Free format text: JAPANESE INTERMEDIATE CODE: A523 Effective date: 20190311
2019-08-02	TRDD	Decision of grant or rejection written	
2019-08-13	A01	Written decision to grant a patent or to grant a registration (utility model)	Free format text: JAPANESE INTERMEDIATE CODE: A01 Effective date: 20190813

2019-09-12	A61	First payment of annual fees (during grant procedure)	Free format text: JAPANESE INTERMEDIATE CODE: A61 Effective date: 20190905
2019-09-19	R150	Certificate of patent or registration of utility model	Ref document number: 6585625 Country of ref document: JP Free format text: JAPANESE INTERMEDIATE CODE: R150
2022-09-24	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250

Concepts

machine-extracted

Download Filter table

Name	Image	Sections	Count	Query match
receptor antagonist		title,claims,abstract,description	91	0.000
Hyperplasia		title,claims,description	10	0.000
Congenital anomaly		title,claims,description	9	0.000
adrenocortical		title,claims,description	9	0.000
CRHR1		title,abstract	3	0.000
CRHR1		title,abstract	3	0.000
Corticotropin-Releasing Hormone		claims,abstract,description	137	0.000
corticotropin		claims,abstract,description	80	0.000
ACTH and synthetic analog preparations		claims,abstract	8	0.000
compounds		claims,description	60	0.000
3-(4-methoxy-2-methylphenyl)-2,5-dimethyl-4-((1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl)pyrazolo[1,5-a]pyrimidin-7-amine		claims,description	39	0.000
17α-hydroxyprogesterone		claims,description	26	0.000
Dissociation Half-Life		claims,description	25	0.000
circadian rhythms		claims,description	21	0.000
circadian rhythm		claims,description	18	0.000
3-[6-(dimethylamino)-4-methylpyridin-3-yl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-a]pyrimidin-7-amine		claims,description	12	0.000
SSR-126374		claims,description	12	0.000
268545-87-5		claims,description	10	0.000
crinecerfont		claims,description	8	0.000

				
methoxydanyl	claims,description	3	0.000	
				
phenyl group	claims,description	3	0.000	
				
propyl group	claims,description	3	0.000	
				
pyrazolo[1,5-a]pyrimidin-7-amine	claims,description	3	0.000	
Adrenogenital Syndrome	claims,description	2	0.000	
Congenital Adrenal Hyperplasia	claims,description	2	0.000	
chronic kidney disease	claims	30	0.000	
1,2,4-oxadiazol-5-yl group	claims	2	0.000	
				
7H-pyrrolo[2,3-d]pyrimidin-4-amine	claims	1	0.000	
				
Cortisol	abstract,description	30	0.000	
hydrocortisone	abstract,description	30	0.000	
antagonistic	abstract,description	23	0.000	
antagonist	abstract,description	23	0.000	
androgen	abstract,description	13	0.000	
manufacturing process	abstract,description	8	0.000	
normalization	abstract,description	4	0.000	
side effect	abstract,description	4	0.000	
VNR048W	abstract	1	0.000	
crf1	abstract	1	0.000	
Show all concepts from the description section				

Data provided by IFI CLAIMS Patent Services

(19) 日本国特許庁 (JP)

(12) 公表特許公報 (A)

(11) 特許出願公表番号

特表2017-503030

(P2017-503030A)

(43) 公表日 平成29年1月26日 (2017.1.26)

(51) Int. Cl.	F I	テーマコード (参考)
A61K 45/00 (2006.01)	A61K 45/00	4C084
A61K 31/519 (2006.01)	A61K 31/519	4C086
A61P 5/38 (2006.01)	A61P 5/38	

審査請求 未請求 予備審査請求 未請求 (全 38 頁)

(21) 出願番号	特願2016-565135 (P2016-565135)	(71) 出願人	398005054 ニューロクライン バイオサイエンス 。インコーポレイテッド アメリカ合衆国 カリフォルニア 921 30, サン ディエゴ, エル カミノ レ アル 12790
(86) (22) 出願日	平成27年1月21日 (2015.1.21)	(74) 代理人	100078282 弁理士 山本 秀策
(85) 翻訳文提出日	平成28年8月24日 (2016.8.24)	(74) 代理人	100113413 弁理士 森下 夏樹
(86) 国際出願番号	PCT/US2015/012315	(72) 発明者	グリゴリアディス, ディミトリ イー. アメリカ合衆国 カリフォルニア 921 30, サンディエゴ, ジンジャーウッ ド コーブ 10626
(87) 国際公開番号	W02015/112642	Fターム (参考)	4C084 AA17 NA14 ZC08 ZC42
(87) 国際公開日	平成27年7月30日 (2015.7.30)		最終頁に続く
(31) 優先権主張番号	61/929, 941		
(32) 優先日	平成26年1月21日 (2014.1.21)		
(33) 優先権主張国	米国 (US)		
(31) 優先権主張番号	61/981, 033		
(32) 優先日	平成26年4月17日 (2014.4.17)		
(33) 優先権主張国	米国 (US)		
(31) 優先権主張番号	62/069, 155		
(32) 優先日	平成26年10月27日 (2014.10.27)		
(33) 優先権主張国	米国 (US)		

(54) 【発明の名称】 先天性副腎皮質過形成の処置のためのCRF1レセプターアンタゴニスト

(57) 【要約】

CRF₁レセプターアンタゴニストは、CAHを有する患者においてACTH放出を直接阻害し、それによって、ヒドロコルチゾンのより低い、より生理学的な用量を使用しながらアンドロゲン生成の正常化を可能にし、従って、処置関連の副作用を低減する能力を有する。一実施形態において、必要性のある被験体に、有効量のCRF₁アンタゴニストを投与する工程（就寝時投与が挙げられる（が、これらに限定されない））によって、CAHを処置するための方法が提供される。

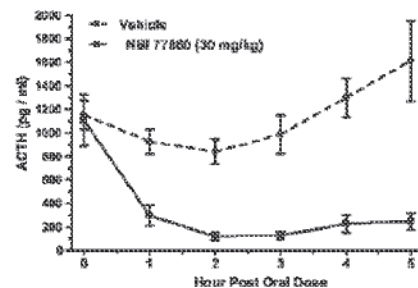


FIG. 2

【特許請求の範囲】

【請求項 1】

30分間を超える解離半減期を有するCRF₁レセプターアンタゴニストを必要性のある被験体に投与する工程によって、先天性副腎皮質過形成(CAH)を処置するための方法。

【請求項 2】

前記CRF₁レセプターアンタゴニストは、40分間を超える解離半減期を有する、請求項1に記載の方法。

【請求項 3】

前記CRF₁レセプターアンタゴニストは、50分間を超える解離半減期を有する、請求項1に記載の方法。

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【請求項 4】

前記CRF₁レセプターアンタゴニストは、化合物I(NBI-77860; 2, 5-ジメチル-3-[2-メチル-4-(メチルオキシ)フェニル]-N-[(1S)-1-(3-メチル-1, 2, 4-オキサジアゾール-5-イル)プロピル]ピラゾロ[1, 5-a]ピリミジン-7-アミン)である、請求項1に記載の方法。

【請求項 5】

前記CRF₁レセプターアンタゴニストは、NBI-30775、NBI-34041、SSR-126374、SSR-125543、アンタラルミン(N-ブチル-N-エチル-2, 5, 6-トリメチル-7-(2, 4, 6-トリメチルフェニル)ピロロ[3, 2-e]ピリミジン-4-アミン)、もしくはDMP904である、請求項1に記載の方法。

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【請求項 6】

前記CRF₁レセプターアンタゴニストは、就寝時に投与される、請求項1～5のいずれか1項に記載の方法。

【請求項 7】

前記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の時にもしくはその前に投与される、請求項1～5のいずれか1項に記載の方法。

【請求項 8】

前記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の3～4時間前に投与される、請求項7に記載の方法。

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【請求項 9】

先天性副腎皮質過形成(CAH)を有する被験体における17-OHPおよびACTHのレベルを低下させるための方法であって、該方法は、該被験体に、CRF₁レセプターアンタゴニストを就寝時に投与する工程を包含する、方法。

【請求項 10】

前記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の時にもしくはその前に投与される、請求項9に記載の方法。

【請求項 11】

前記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の3～4時間前に投与される、請求項9に記載の方法。

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【請求項 12】

前記CRF₁レセプターアンタゴニストは、化合物I(NBI-77860; 2, 5-ジメチル-3-[2-メチル-4-(メチルオキシ)フェニル]-N-[(1S)-1-(3-メチル-1, 2, 4-オキサジアゾール-5-イル)プロピル]ピラゾロ[1, 5-a]ピリミジン-7-アミン)である、請求項9～11のいずれか1項に記載の方法。

【請求項 13】

前記CRF₁レセプターアンタゴニストは、NBI-30775、NBI-34041、SSR-126374、SSR-125543、アンタラルミン(N-ブチル-N-エ

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チル-2, 5, 6-トリメチル-7-(2, 4, 6-トリメチルフェニル)ピロロ[3, 2-e]ピリミジン-4-アミン)、もしくはDMP904である、請求項9～11のいずれか1項に記載の方法。

【請求項14】

先天性副腎皮質過形成(CAH)を処置するにあたって使用するためのCRF₁レセプターアンタゴニストであって、ここで該CRF₁レセプターアンタゴニストは、30分間を超える解離半減期を有する、CRF₁レセプターアンタゴニスト。

【請求項15】

前記CRF₁レセプターアンタゴニストは、40分間を超える解離半減期を有する、請求項14に記載のCRF₁レセプターアンタゴニスト。

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【請求項16】

前記CRF₁レセプターアンタゴニストは、50分間を超える解離半減期を有する、請求項14に記載のCRF₁レセプターアンタゴニスト。

【請求項17】

前記CRF₁レセプターアンタゴニストは、化合物I(NBI-77860: 2, 5-ジメチル-3-[2-メチル-4-(メチルオキシ)フェニル]-N-[(1S)-1-(3-メチル-1, 2, 4-オキサジアゾール-5-イル)プロピル]ピラゾロ[1, 5-a]ピリミジン-7-アミン)である、請求項14に記載のCRF₁レセプターアンタゴニスト。

【請求項18】

前記CRF₁レセプターアンタゴニストは、NBI-30775、NBI-34041、SSR-126374、SSR-125543、アンタラルミン(N-ブチル-N-エチル-2, 5, 6-トリメチル-7-(2, 4, 6-トリメチルフェニル)ピロロ[3, 2-e]ピリミジン-4-アミン)、もしくはDMP904である、請求項14に記載のCRF₁レセプターアンタゴニスト。

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【請求項19】

前記CRF₁レセプターアンタゴニストは、就寝時に投与するために適している、請求項14～18のいずれか1項に記載のCRF₁レセプターアンタゴニスト。

【請求項20】

前記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の時にもしくはその前に投与するために適している、請求項14～18のいずれか1項に記載のCRF₁レセプターアンタゴニスト。

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【請求項21】

前記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の3～4時間前に投与するために適している、請求項14～18のいずれか1項に記載のCRF₁レセプターアンタゴニスト。

【発明の詳細な説明】

【技術分野】

【0001】

(背景)

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(技術分野)

先天性副腎皮質過形成を処置するための組成物および方法が、本明細書で記載される。

【背景技術】

【0002】

(関連技術の説明)

先天性副腎皮質過形成(CAH)は、コルチゾール生合成をほとんどもしくは全く生じない常染色体劣性遺伝障害の一群である。上記疾患の最も頻度の高い形態は、CAH症例のうちの約95%を占める、染色体6p21に位置するCYP21A2遺伝子における変異によって引き起こされる21-ヒドロキシラーゼ欠損である(総説に関しては、例えば、Speiser et al., Int. J. Pediatr. Endocr

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inol. 2010:494173 (2010)を参照のこと)。これら変異は、特定の変異の直接的結果である疾患重症度を生じる、副腎皮質におけるコルチゾール合成に必要とされる酵素活性の完全な喪失からある範囲の部分的喪失までの範囲に及び得る。21-ヒドロキシラーゼ欠損のこの連続型は、塩類喪失形態および単純男性化形態(古典的CAHとしてグループ分けされる)、ならびに非古典的CAH(NCCAH)もしくは「遅発性」CAHとして公知の、より軽度の形態(これは通常、後期小児期もしくは早期成人期に診断される)へと広く分類されてきた。非古典的CAH患者は、ホモ接合性もしくはしばしば、古典的CAH対立遺伝子を伴って、複合ヘテロ接合体のいずれかを有する。これら患者は、十分な酵素活性(正常の>20~50%)を有し、その結果、彼らは塩類喪失もしくはコルチゾール欠損を有さず、誕生時に正常な外性器を有し、そして多くは、生涯を通じて無症候性のままである(Trapp et al., Steroids 77(4):342-46 (2012))。上記疾患の頻度の少ない形態(これは症例のうちの5%を占める)では、11β-ヒドロキシラーゼ遺伝子CYP11B1の変異が、CAH(11β-OH CAH)を生じる。

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両方の遺伝的変異は、アンドロゲンの過剰生成とともに、先天性副腎皮質過形成、コルチゾール欠損および過剰な副腎皮質刺激ホルモン(ACTH)生成を生じる。これら患者には、グルココルチコイドでの終生の管理およびこのような処置と関連して付随する問題が要求される。よって、健康状態、幸福、クオリティ・オブ・ライフを改善するために、およびCAHを有する患者における関連障害を管理するために、処置レジメンが非常に必要である。

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【先行技術文献】

【非特許文献】

【0003】

【非特許文献1】Speiser et al., Int. J. Pediatr. Endocrinol. 2010:494173 (2010)

【非特許文献2】Trapp et al., Steroids 77(4):342-46 (2012)

【発明の概要】

【課題を解決するための手段】

【0004】

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(要旨)

副腎皮質刺激ホルモン放出因子(CRF)は、クラスB Gプロテイン共役レセプター(GPCR)であるCRF₁レセプターを活性化する。CRF₁アンタゴニストは、CAHを有する患者におけるACTH放出を直接阻害し、それによって、ヒドロコルチゾンのより低い、より生理学的な用量を使用しながらアンドロゲン生成の正常化を可能にし、処置関連副作用を低減する能力を有する。

【0005】

一実施形態において、必要性のある被験体に、有効量のCRF₁アンタゴニストを投与する工程(就寝時投与が挙げられる(が、これらに限定されない))によって、CAHを処置するための方法が提供される。

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【0006】

より具体的な実施形態において、上記CRF₁アンタゴニストは、30分間を超える、および別の実施形態では40分間を超える、および別の実施形態では50分間を超える解離半減期($t_{1/2}$)を有する。

【0007】

実施形態1 30分間を超える解離半減期を有するCRF₁レセプターアンタゴニストを必要性のある被験体に投与する工程によって、先天性副腎皮質過形成(CAH)を処置するための方法。

【0008】

実施形態2 前記CRF₁レセプターアンタゴニストは、40分間を超える解離半減期

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を有する、実施形態1に記載の方法。

【0009】

実施形態3 前記CRF₁レセプターアンタゴニストは、50分間を超える解離半減期を有する、実施形態1に記載の方法。

【0010】

実施形態4 前記CRF₁レセプターアンタゴニストは、化合物I (NBI-77860; 2, 5-ジメチル-3-[2-メチル-4-(メチルオキシ)フェニル]-N-[(1S)-1-(3-メチル-1, 2, 4-オキサジアゾール-5-イル)プロピル]ピラゾロ[1, 5-a]ピリミジン-7-アミン)である、実施形態1~3のいずれか1つに記載の方法。

【0011】

実施形態5 前記CRF₁レセプターアンタゴニストは、NBI-30775、NBI-34041、SSR-126374、SSR-125543、アンタラルミン(N-ブチル-N-エチル-2, 5, 6-トリメチル-7-(2, 4, 6-トリメチルフェニル)ピロロ[3, 2-e]ピリミジン-4-アミン)、もしくはDMP904である、実施形態1~3のいずれか1つに記載の方法。

【0012】

実施形態6 前記CRF₁レセプターアンタゴニストは、就寝時に投与される、実施形態1~5のいずれか1つに記載の方法。

【0013】

実施形態7 前記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の時にもしくはその前に投与される、実施形態1~6のいずれか1つに記載の方法。

【0014】

実施形態8 前記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の3~4時間前に投与される、実施形態7に記載の方法。

【0015】

実施形態9 先天性副腎皮質過形成(CAH)を有する被験体における17-OHPおよびACTHのレベルを低下させるための方法であって、該方法は、該被験体に、CRF₁レセプターアンタゴニストを就寝時に投与する工程を包含する、方法。

【0016】

実施形態10 前記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の時にもしくはその前に投与される、実施形態9に記載の方法。

【0017】

実施形態11 前記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の3~4時間前に投与される、実施形態9または実施形態10に記載の方法。

【0018】

実施形態12 前記CRF₁レセプターアンタゴニストは、化合物I (NBI-77860; 2, 5-ジメチル-3-[2-メチル-4-(メチルオキシ)フェニル]-N-[(1S)-1-(3-メチル-1, 2, 4-オキサジアゾール-5-イル)プロピル]ピラゾロ[1, 5-a]ピリミジン-7-アミン)である、実施形態9~11のいずれか1つに記載の方法。

【0019】

実施形態13 前記CRF₁レセプターアンタゴニストは、NBI-30775、NBI-34041、SSR-126374、SSR-125543、アンタラルミン(N-ブチル-N-エチル-2, 5, 6-トリメチル-7-(2, 4, 6-トリメチルフェニル)ピロロ[3, 2-e]ピリミジン-4-アミン)、もしくはDMP904である、実施形態9~11のいずれか1つに記載の方法。

【0020】

実施形態14 先天性副腎皮質過形成 (CAH) を処置するにあたって使用するための CRF₁ レセプターアンタゴニストであって、ここで該 CRF₁ レセプターアンタゴニストは、30分間を超える解離半減期を有する、CRF₁ レセプターアンタゴニスト。

【0021】

実施形態15 前記 CRF₁ レセプターアンタゴニストは、40分間を超える解離半減期を有する、14に記載の CRF₁ レセプターアンタゴニスト。

【0022】

実施形態16 前記 CRF₁ レセプターアンタゴニストは、50分間を超える解離半減期を有する、実施形態14に記載の CRF₁ レセプターアンタゴニスト。

【0023】

実施形態17 前記 CRF₁ レセプターアンタゴニストは、化合物 I (NBI-77860; 2, 5-ジメチル-3-[2-メチル-4-(メチルオキシ)フェニル]-N-[(1S)-1-(3-メチル-1, 2, 4-オキサジアゾール-5-イル) プロピル] ピラゾロ [1, 5-a] ピリミジン-7-アミン) である、実施形態14~16のいずれか1つに記載の CRF₁ レセプターアンタゴニスト。

【0024】

実施形態18 前記 CRF₁ レセプターアンタゴニストは、NBI-30775、NBI-34041、SSR-126374、SSR-125543、アンタラルミン (N-ブチル-N-エチル-2, 5, 6-トリメチル-7-(2, 4, 6-トリメチルフェニル) ピロロ [3, 2-e] ピリミジン-4-アミン)、もしくは DMP904 である、実施形態14~16のいずれか1つに記載の CRF₁ レセプターアンタゴニスト。

【0025】

実施形態19 前記 CRF₁ レセプターアンタゴニストは、就寝時に投与するために適している、実施形態14~18のいずれか1つに記載の CRF₁ レセプターアンタゴニスト。

【0026】

実施形態20 前記 CRF₁ レセプターアンタゴニストは、予測される概日リズムによる ACTH 放出の時にはしくはその前に投与するために適している、実施形態14~19のいずれか1つに記載の CRF₁ レセプターアンタゴニスト。

【0027】

実施形態21 前記 CRF₁ レセプターアンタゴニストは、予測される概日リズムによる ACTH 放出の3~4時間前に投与するために適している、実施形態14~20のいずれか1つに記載の CRF₁ レセプターアンタゴニスト。

【0028】

他の実施形態において、上記でおよび本明細書に記載される方法および使用は、グルココルチコイドもしくは鉱質コルチコイドの量を、CAHを有する成熟した (full grown) 被験体 (例えば、ヒト被験体) に投与される GC (例えば、ヒドロコルチゾン (HC)、プレドニゾン、プレドニゾロン、デキサメタゾン、もしくはフルドロコルチゾン) の推奨される1日用量から、少なくとも10%、15%、20%、30%、40%、50%、60%低減する工程をさらに包含する。他の実施形態において、上記でおよび本明細書に記載される方法および使用は、グルココルチコイドもしくは鉱質コルチコイドの量を、CAHを有する成長中の被験体 (例えば、ヒト被験体) に投与される GC (例えば、ヒドロコルチゾン) もしくは鉱質コルチコイド (例えば、フルドロコルチゾン) の推奨される1日用量から、少なくとも10%、15%、20%、30%、40%、50%、60%低減する工程をさらに包含する。

【0029】

これらおよび他の実施形態は、以下の詳細な説明を参照すれば明らかである。この目的に向けて、ある種の背景情報、手順、化合物および組成物をより詳細に記載する種々の参考文献は、本明細書で示され、それらの全体において各々が本明細書に参考として援用される。

【0030】

本明細書で具体的に定義されない用語は、本開示および状況に鑑みて、当業者によって上記用語に与えられる意味が与えられるものとする。しかし、本明細書で使用される場合、それとは逆に特定されなければ、上記用語は、示される意味を有する。本明細書全体を通じて「一実施形態」もしくは「ある（一）実施形態」への言及は、上記実施形態に関連して記載される特定の特徵、構造もしくは特性が少なくとも一実施形態に含まれることを意味する。従って、本明細書全体を通じて種々の場所における語句「一実施形態において」もしくは「ある（一）実施形態において」との出現は、全てが必ずしも同じ実施形態をいうわけではない。さらに、上記特定の特徵、構造、もしくは特性は、1以上の実施形態において任意の適切な様式で組み合わせられ得る。

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【0031】

また、本明細書および添付の特許請求の範囲で使用される場合、単数形「a（1つの、ある）」、「an（1つの、ある）」および「the（上記、この、その、）」とは、状況が明らかに別のことを指し示さなければ、複数形への言及をも含む。従って、例えば、「a non-human animal（ある非ヒト動物）」への言及は、1以上の非ヒト動物、もしくは複数のこのような動物に言及し得、「a cell（1つの細胞）」もしくは「the cell（上記細胞）」への言及は、1以上の細胞および当業者に公知のその均等物（例えば、複数の細胞）への言及を含むなど。方法の工程が記載されるかもしくは特許請求され、上記工程が特定の順序で起こると記載される場合、第2の工程「より前に」（すなわち、その前に）起こる（もしくは行われる）第1の工程の記載は、上記第2の工程が上記第1の工程に「引き続いて」起こる（もしくは行われる）という状態に書き換えられる場合には同じ意味を有する。用語「about（約、およそ）」とは、数もしくは数値範囲に言及する場合、この言及される数もしくは数値範囲が、実験上の変動性の内にある（もしくは統計上の実験誤差の内にある）近似値であり、従って、その数字もしくは数値範囲が、述べられた数もしくは数値範囲の1%～15%の間で変動し得ることを意味する。用語「or（あるいは、または、もしくは）」は一般に、状況が明らかに別のことを指し示さなければ、「and/or（および／または）」を含むその意味で使用されることにも注意するものとする。用語「at least one（少なくとも1）」とは、例えば、少なくとも1種の化合物もしくは少なくとも1種の組成物に言及する場合、用語「one or more（1以上）」と同じ意味および理解を有する。

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【図面の簡単な説明】

【0032】

【図1】図1は、副腎におけるステロイド合成経路の模式図を示す。CAHの最も一般的な形態は、21-ヒドロキシラーゼ（21- α -ヒドロキシラーゼともいわれる）欠損によって引き起こされ、コルチゾールの減少およびアンドロゲン（例えば、テストステロンおよびエストロゲン）の増大を生じる。古典的CAHのより希なタイプは、11 β -ヒドロキシラーゼ欠損である。

【0033】

【図2】図2は、副腎摘出ラットにおけるACTH濃度に対する化合物I（NBI-77860）の効果を図示するグラフを表す。ラットに、30mg/kgの化合物I（NBI-77860）を経口的に与えた。データを、ACTHの平均血漿濃度（ $\pm$ SEM）として表す。

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【0034】

【図3】図3A～Cは、CRF₁レセプターアンタゴニストの、副腎摘出ラットにおけるACTH濃度に対する効果（それらの解離半減期によって区別される）を図示するグラフを表す。

【0035】

【図4】図4は、NBI-77860の安全性、寛容性および血漿曝露を評価するために設計された、実施例6に記載される臨床試験の研究デザイン模式図、ならびにHPA（視床下部-下垂体-副腎）系ホルモンの内因性レベルに対するこの化合物の効果を表す。

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【0036】

【図5】図5は、実施例6に記載される臨床試験の間の、投与後24時間期間の間中の平均17-OHP（上のパネル）およびACTHレベル（下のパネル）のデータを表す。

【0037】

【図6】図6は、300mgおよび600mgのNBI-77860ならびにプラセボの投与後の経時的な17-OHP（上パネル）およびACTHレベル（下パネル）に関する具体的な個々の被験体の応答を表す。

【発明を実施するための形態】

【0038】

（詳細な説明）

本明細書で記載されるように、CRF₁レセプターアンタゴニストは、CAHを有する患者におけるACTH放出を直接阻害し、それによって、アンドロゲン生成の正常化を可能にすることが見出された。CRF₁レセプターアンタゴニストの投与は、CAHを有する被験体においてヒドロコルチゾンのより低い、より生理学的な用量の使用を可能にし、従って、処置関連副作用を低減する。

【0039】

CAHの新生児スクリーニングは、生後72時間以内に得られるヒールスティック毛細管血液標本において17-OHPレベルを測定するイムノアッセイによって行われる。上記血液サンプルを、市販の解離増強ランタニド蛍光イムノアッセイ（DELFLIA; PerkinElmer, Waltham Massachusetts）（White et al., J. Pediatr. 163:10-12 (2013)）によって、17-OHPについて分析する。

【0040】

生化学的試験法および分子遺伝学的試験法を利用して生後8～14日間の間に行われる二番手のスクリーニング試験は、米国の9つの州が使用しており、さらに5つの州が強く推奨している。上記生化学的方法としては、有機溶媒抽出物を用いたイムノアッセイもしくは液体クロマトグラフィー、続いて、コルチゾールに対する17-OHP、アンドロステンジオン、および21-デオキシコルチゾールのステロイド比を測定するためのタンデム質量分析法が挙げられる（例えば、Speiser et al., Int. J. Pediatr. Endocrinol. 2010:494173, 2010を参照のこと）。遺伝子スクリーニングは、CAHと関連するCYP21A2変異を調べる。米国で広く使用されているわけではないが、第2のスクリーニングを追加することで、スクリーニングプロセス全体の感度（ここで第1のスクリーニングのみでは約72%である）を潜在的に改善できた。

【0041】

新生児スクリーニングの結果がなければ、古典的CAHを有する幼い女兒は、代表的には、性別が曖昧な外性器の存在に起因して同定される。男性は、生まれたときに正常な外性器を有するので、新生児スクリーニングが行われなければ、または他の医学的合併症に気づかなければ、診断されない。CAHと最初に診断されず、この疾患の塩類喪失形態を経験する幼児は、生後数週間以内に体重増大が不十分、嘔吐、高カリウム血症および低ナトリウム血症という状況の中で後に診断される。

【0042】

CAHの処置は、幼年期から成人期における診断から種々の薬物療法を使用するホルモンおよびステロイドレベルの正常化に基づく。グルココルチコイドは、CAHでは現在標準的な処置であり、内因性コルチゾール欠損を矯正する、および下垂体からのACTHレベル上昇（これは、アンドロゲン生成増大を駆動する）を低減する、両方のために使用される。コルチゾール補充（cortisol replacement）が十分であるアジソン病（副腎機能低下）の処置とは異なり、CAHの処置は、ACTH生成も低減して、その後のアンドロゲン過剰をも制御しなければならない。従って、グルココルチコイド処置の目標は、女性においては男性化および月経障害を防止するために、ならびに男性に

においては精巣副腎残存腫瘍 (testicular adrenal rest tumor) を阻害するために、コルチゾール補充およびACTHの抑制を含む。鉱質コルチコイド補充は、CAHの塩類喪失形態を有するそれら患者において通常血圧、電解質バランス、および容積状態の維持のための正常の血漿レニン活性を達成するために必要とされる。

【0043】

グルココルチコイド処置のレジメンは、正常な生理機能を支援し、そしてまた、強いストレス応答 (例えば、併発疾患、運動、低血圧) を誘発し得る事象の間に十分なコルチゾールが利用可能であることを担保しなければならない。アンドロゲン生成を十分に抑制しようとしてグルココルチコイド過剰処置になることに起因する医原性クッシング症候群、または処置不十分に起因するアジソン症候群の発生を回避するためには、注意深いモニタリングもまた必要である。鉱質コルチコイドでの過剰処置は、高血圧症を引き起こし得る一方で、処置不十分は、低血圧、塩類喪失、疲労およびグルココルチコイドの要求の増大をもたらし得る。処置の効力をモニターするための代表的な実験室での検査としては、17-OHP、アンドロステンジオン、テストステロン、レニン活性、および電解質の血漿濃度の測定が挙げられる。

【0044】

CAHを有する成人患者は、肥満、高血圧症、およびインスリン抵抗性を含む心血管疾患のリスク因子の増大した保有率を有する (例えば、Kim et al., Semin. Reprod. Med. 27 (4): 316-21 (2009) を参照のこと)。小児および成人のCAH患者 (n=244) の大コホート研究から、患者は、種々のグルココルチコイド処置レジメンを処方されるにも関わらず、不十分なホルモン制御および前述の有害転帰を頻繁に経験していることが示された (例えば、Finkelstein et al., J. Clin. Endocrinol Metab. 97 (12): 4429-38 (2012) を参照のこと)。

【0045】

CAHの処置は、グルココルチコイド (通常は、小児ではヒドロコルチゾンであるが、成人では、デキサメタゾンのような、しばしば治療指数の狭いより強力な薬剤)、および塩類喪失に必要であれば、鉱質コルチコイド (通常はフルドコルチゾン) でのコルチゾール欠損を正常化する試みを含む。しかし、過剰なアンドロゲンの十分な抑制を達成するために必要とされるグルココルチコイド用量は、通常は、アジソン病を有する患者におけるように、コルチゾール補充のみに使用される通常の生理学的用量を十分に上回っている。グルココルチコイドへのこの増大した曝露は、CAH患者において、医原性クッシング症候群、心血管リスク因子の増大、耐糖能障害、および骨密度 (bone mineral density) の低下をもたらす (例えば、Elneceave 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) を参照のこと)。

【0046】

副腎皮質刺激ホルモン放出因子 (CRF) を、ヒツジ視床下部から単離し、41アミノ酸のペプチドとして同定した。CRFは、内分泌系、神経系、および免疫系の機能において顕著な変化を生じることが見出された。CRFは、副腎皮質刺激ホルモン (「ACTH」)、 β -エンドルフィン、および他のプロオピオメラノコルチン (「POMC」) (下垂体前葉由来ペプチド) の基底の放出およびストレス誘発性の放出の主要な生理学的調節因子であると考えられる (例えば、Vale et al., Science 213: 1394-1397, 1981を参照のこと)。CRFの分泌は、Gプロテイン共役レセプターのクラスBファミリーのメンバーであるCRF₁レセプターへの結合を介して、下垂体前葉における副腎皮質刺激ホルモン生成細胞 (corticotroph) から

のACTH放出を引き起こす。

【0047】

CRFの生理学的重要性に起因して、顕著なCRF₁レセプター結合活性を有しかつ上記CRF₁レセプターに拮抗できる生物学的に活性な低分子の開発は、未だに望まれる目標であり、不安、鬱病、過敏性腸症候群、心的外傷後ストレス障害、および物質乱用の処置のために進行中の研究および開発の主題であり続けている。

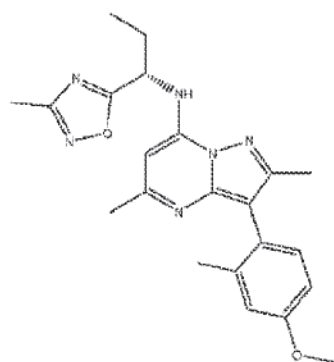
【0048】

下垂体ホルモンACTHは、視床下部の副腎皮質刺激ホルモン放出因子(CRF)の制御下にあり、コレステロールの取り込みを刺激し、副腎におけるステロイド生成を開始するプレグネノロンの合成を駆動する(図1を参照のこと)。副腎皮質は、3つのゾーンから構成され、これらは、ホルモンの別個のクラスを生成し、そのうちの多くは、この経路を介してコレステロールを動員させるACTHによって駆動される。変異もしくは欠失の結果としてのこれら酵素の欠損は、基質濃度の増大を引き起こす。21-ヒドロキシラーゼ遺伝子(CYP21A2)における変異もしくは欠失から生じるCAHの最も一般的な形態では、ステロイド前駆体である、プロゲステロンおよび17-ヒドロキシプロゲステロン(17-OHP)の蓄積が原因で、強力なアンドロゲンが副腎によって生成される。17-OHPの血漿レベルは、これら症例において正常濃度の10~1000倍にも達し得る。これら増大は、アンドロゲン、具体的には、アンドロステンジオン、テストステロン、およびジヒドロキシテストステロンの過剰生成を生じ、女性において男性化を引き起こす。さらに、CAHにおける21-ヒドロキシラーゼ欠損は、グルココルチコイドおよび鉱質コルチコイド、具体的にはコルチゾールおよびアルドステロンの不十分な生成を引き起こす。コルチゾールは、視床下部のCRF分泌および下垂体のACTH放出の重要なネガティブフィードバック調節因子である。グルココルチコイド合成および放出の欠如は、視床下部および下垂体に対する抑制を排除し、このことは、ACTHレベルを増大させる。過剰なACTH刺激は、索状帯および網状帯の肥大を引き起こし、副腎過形成を生じる。

【0049】

一実施形態において、CAHの処置に有用なCRF₁レセプターアンタゴニストは、NB1-77860、2, 5-ジメチル-3-[2-メチル-4-(メチルオキシ)フェニル]-N-[(1S)-1-(3-メチル-1, 2, 4-オキサジアゾール-5-イル)プロピル]ピラゾロ[1, 5-a]ピリミジン-7-アミン(本明細書で「化合物1」ともいわれる)であり、これは、以下の構造を有する。

【化1】



化合物1

【0050】

化合物1は、結合 $pK_i=8.2$ を有する強力なCRF₁アンタゴニストである(例えば、Tellew et al., Bioorg. Med. Chem. Lett., 20:7259, 2010および国際特許出願公開番号WO 2006/0449

58（これらはともに、それらの全体において本明細書に参考として援用される）を参照のこと）。本明細書で記載されるとおり、化合物Iは、副腎摘出ラットにおいて示されるように強力なACTH低下効果を有する。

【0051】

別の実施形態において、CAHの処置に有用なCRF₁レセプターアンタゴニストは、米国特許第6,586,456号、同第6,806,282号、同第6,531,475号、同第6,664,261号、同第6,610,678号、WO 98/08846、WO 98/11075、WO 99/10350、WO 2000/059888、WO 2006/044821、WO 2006/102194、WO 2006/107784、WO 2006/116412、WO 2006/126718、WO 2007/069565、WO 2007/069671、WO 2008/036541、WO 2008/036579、WO 2008/051533、WO 2008/082003、WO 2008/083070、WO 2008/136377、WO 2009/008552、WO 2009/144632、WO 2010/014280、WO 2010/014687、WO 2010/015628、WO 2010/015655、WO 2010/062718、WO 2010/096426、WO 2011/043387、WO 2011/092293、WO 2011/095450、WO 2011/092290、およびWO 2011/043381に記載されるとおりの低分子アンタゴニストである。

【0052】

さらに別の実施形態において、上記CRF₁レセプターアンタゴニストは、NBI-30775、CP-316,311、ペキサセルホント、エミセルホント（emicerfont）、SSR-125543 [4-（2-クロロ-4-メトキシ-5-メチルフェニル）-N-〔（1S）-2-シクロプロピル-1-（3-フルオロ-4-メチルフェニル）エチル]-5-メチル-N-（2-プロピン-1-イル）-2-チアゾールアミン]、SSR-126374、ONO-2333、NBI-34041、JNJ-19567470、GSK586529、PF-00572778、CP-376395、アンタラルミン（N-ブチル-N-エチル-2,5,6-トリメチル-7-（2,4,6-トリメチルフェニル）ピロロ[3,2-e]ピリミジン-4-アミン）、およびDMP904である。

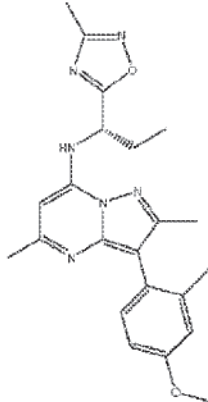
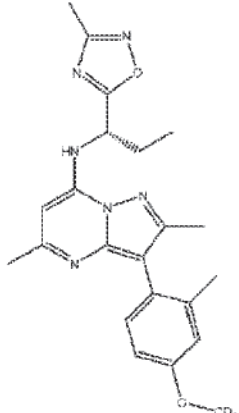
【0053】

なお別の実施形態において、上記CRF₁レセプターアンタゴニストは、30分間を超える、および別の実施形態では40分間を超える、および別の実施形態では50分間を超える解離半減期（ $t_{1/2}$ ）を有する。特定のCRF₁レセプターアンタゴニストの解離半減期は、実施例3で開示される技術によって決定される。これら実施形態の代表的CRF₁レセプターアンタゴニストとしては、化合物I、NBI-30775、NBI-34041、SSR-125543A、アンタラルミン（N-ブチル-N-エチル-2,5,6-トリメチル-7-（2,4,6-トリメチルフェニル）ピロロ[3,2-e]ピリミジン-4-アミン）、およびDMP904が挙げられる。

【0054】

本明細書で記載される化合物に関しては、特定の位置が水素と指定される場合、そのような水素（H）は、重水素（D）で置換され得ることもまた、理解されるものとする。水素の代わりに重水素を組み込むことは、その置換された化合物の生理学的活性および薬理学的活性に対して顕著な効果を生じることが公知である。この目的に向けて、水素の重水素置換は、その位置における重水素存在量（abundance）が天然の重水素存在量より実質的に大きいことを意味するということは、理解されるはずである。よって、一実施形態において、代表的化合物としては、以下が挙げられる。

【化 2 - 1】

化合物	構造	化学名
NBI-77860		2,5-ジメチル-3-[2-メチル-4-(メチルオキシ)フェニル]-N-[(1S)-1-(3-メチル-1,2,4-オキサジアゾール-5-イル)プロピル]ピラゾロ[1,5-a]ピリミジン-7-アミン
重水素化 NBI-77860		2,5-ジメチル-3-[2-メチル-4-(d ₃ -メチルオキシ)フェニル]-N-[(1S)-1-(3-メチル-1,2,4-オキサジアゾール-5-イル)プロピル]ピラゾロ[1,5-a]ピリミジン-7-アミン

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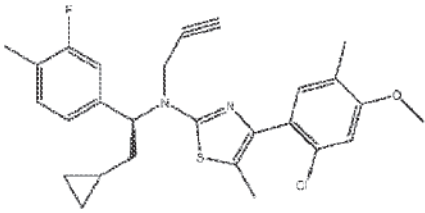
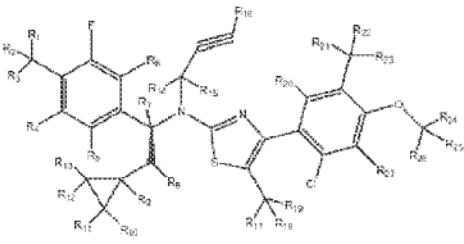
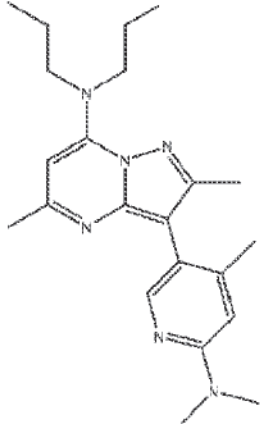
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【化 2 - 3】

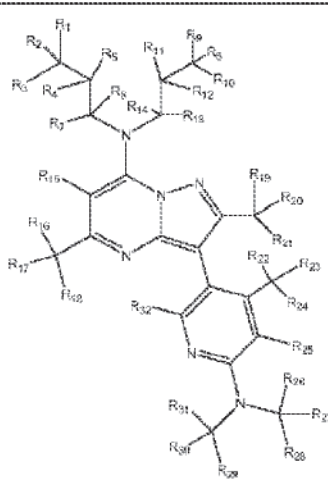
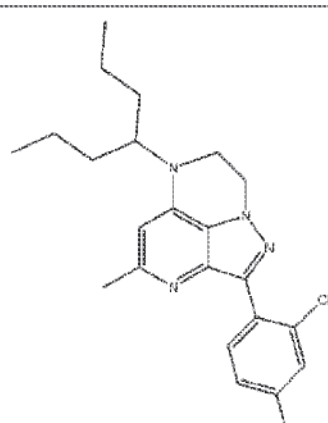
化合物	構造	化学名
	R ₁ -R ₂₆ は、独立してHもしくはD	
SSR-125543		4-(2-クロロ-4-メトキシ-5-メチルフェニル)-N-[(1S)-2-シクロプロピル-1-(3-フルオロ-4-メチルフェニル)エチル]-5-メチル-N-(2-プロピン-1-イル)-2-チアゾールアミン
重水素化 SSR-125543	 <p>R₁-R₂₇は、独立してHもしくはD</p>	
NBI-30775		5-[7-(ジプロピルアミノ)-2,5-ジメチルピラゾロ[1,5-a]ピリミジン-3-イル]-N,N,4-トリメチルピリジン-2-アミン

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【化 2 - 4】

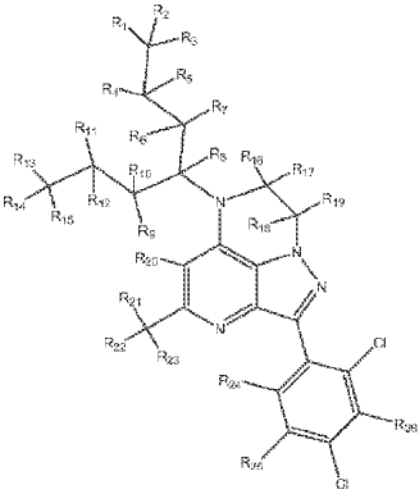
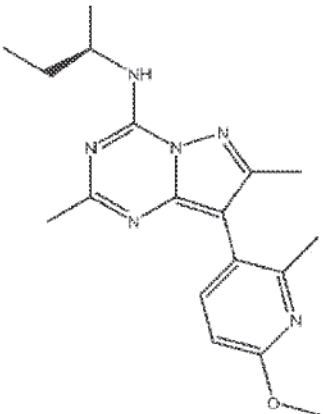
化合物	構造	化学名
重水素化 NBI-30775	 <p>R₁-R₃₂は、独立してHもしくはD</p>	
NBI-34041		3-(2,4-ジクロロフェニル)-9-(ヘプタン-4-イル)-6-メチル-1,2,5,9-テトラアザトリシクロ[6.3.1.0 ^{4,12}]ドデカ-2,4(12),5,7-テトラエン

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【化 2 - 5】

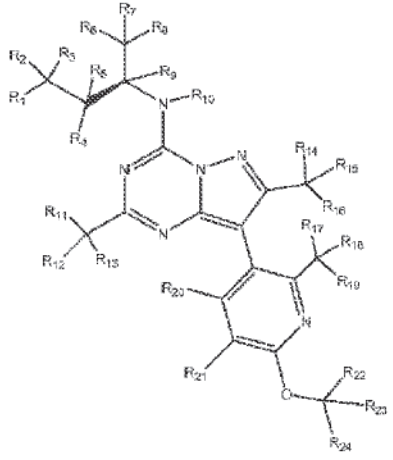
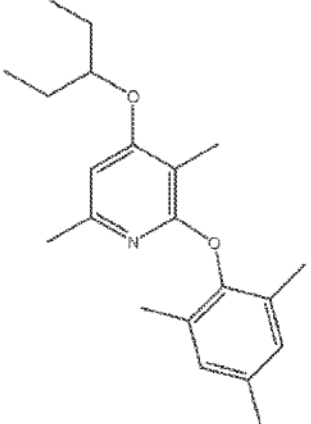
化合物	構造	化学名
重水素化 NBI-34041	 <p>R₁-R₂₆は、独立してHもしくはD</p>	
ベキサセルホント		N-[(2R)-ブタン-2-イル]-8-(6-メトキシ-2-メチルピリジン-3-イル)-2,7-ジメチルピラゾロ[1,5-a][1,3,5]トリアジン-4-アミン

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【化 2 - 6】

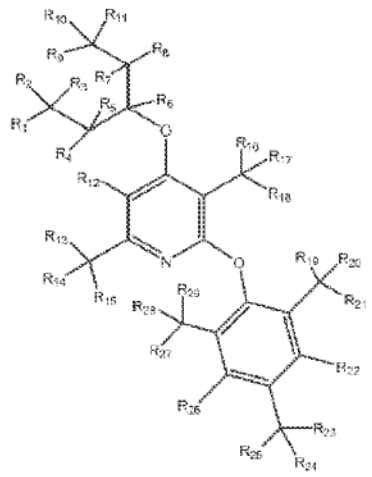
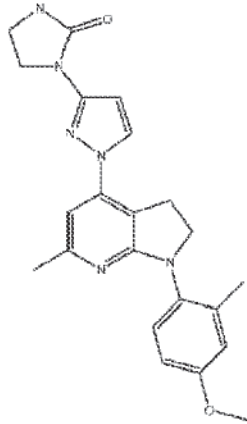
化合物	構造	化学名
重水素化 ベキサセルホント	 <p>R₁-R₂₄は、独立してHもしくはD</p>	
CP-316,311		3,6-ジメチル-4-(ペンタン-3-イルオキシ)-2-(2,4,6-トリメチルフェノキシ)ピリジン

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【化 2 - 7】

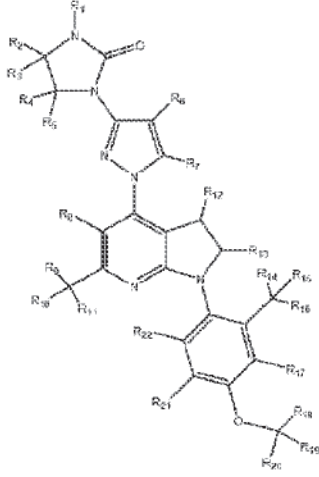
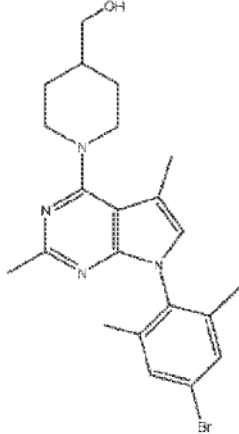
化合物	構造	化学名
重水素化 CP-316,311	 <p>R₁-R₂₉は、独立してHもしくはD</p>	
GSK876008		

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【化 2 - 8】

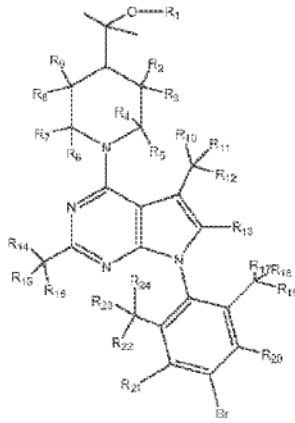
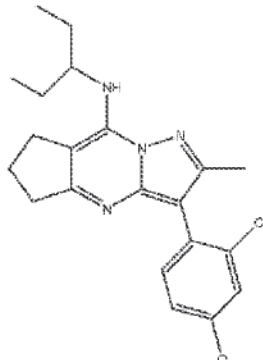
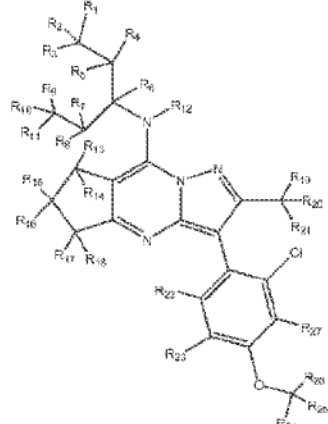
化合物	構造	化学名
重水素化 GSK876008	 <p>R₁-R₂₂は、独立してHもしくはD</p>	
CRA5626/R3 17573		

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【化 2 - 9】

化合物	構造	化学名
重水素化 CRA5626/R3 17573	 <p>R₁-R₂₄は、独立してHもしくはD</p>	
ONO2333Ms		10-(2-クロロ-4-メトキシフェニル)-11-メチル-N-(ペンタン-3-イル)-1,8,12-トリアザトリンクロ [7.3.0.0 ^{3,7}]ドデ カ-2,7,9,11-テトラエン-2-アミン
重水素化 ONO2333	 <p>R₁-R₂₇は、独立してHもしくはD</p>	

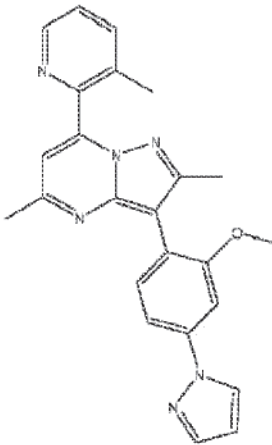
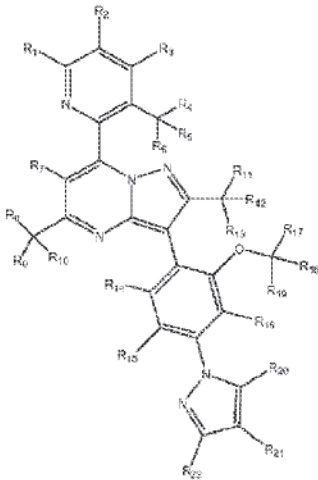
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【化 2 - 1 0】

化合物	構造	化学名
NBI76169		
重水素化 NBI76169	 R ₁ -R ₂₂ は、独立してHもしくはD	

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【0 0 5 5】

別の実施形態において、前述の化合物のうちのいずれも、安定なもしくは放射活性な同位体を組み込み得る。よって、本明細書で記載されるものに同一な同位体標識された化合物の使用もまた企図され、ここで1個以上の原子は、天然において通常見出されるある原子質量もしくは質量数とは異なる原子質量もしくは質量数を有する原子によって置換される。これら化合物へと組み込まれ得る同位体の例としては、水素、炭素、窒素、酸素、リン、フッ素および塩素の同位体、例えば、それぞれ、上記で考察されたとおりの重水素（²H）、ならびに³H、¹³C、¹⁴C、¹⁵N、¹⁸O、¹⁷O、³¹P、³²P、³⁵S、¹⁸F、および³⁶Clが挙げられるが、それに限定されない。ある種の同位体標識された化合物、例えば、³Hおよび¹⁴Cのような放射活性同位体が組み込まれているものはまた、薬物もしくは基質組織分布アッセイにおいて有用である。トリチウム水素（³H）および炭素14（¹⁴C）同位体は、それらの準備および検出可能性の容易さのために特に好ましい。より重い同位体（例えば、重水素（²H））での置換は、より大きな代謝安定性、例えば、インビボ半減期の増大もしくは用量要求の低下から生じるある種の治療的利点を提供し得、従って、いくつかの環境では好ましい可能性がある。同位体標識

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した化合物は一般に、当該分野で慣用的に実施される手順を行うことによって調製され得る。

(副腎摘出ラットにおける血漿ACTHに対する効果)

【0056】

副腎摘出は、ラットにおいて循環コルチコステロン(主なグルココルチコイド)を排除し、視床下部および下垂体(副腎皮質ホルモン生成細胞)両方のレベルにおいてHPA系のネガティブフィードバック制御を除去し、従って、血漿ACTHを慢性的に上昇させる(例えば、Mims et al., J. Natl. Med. Assoc. 69:145-47 (1977)を参照のこと)。ペプチドCRF₁レセプターアンタゴニストの静脈内注射は、副腎摘出(ADX)ラットにおける高い血漿ACTHレベルを低下させることが示された(例えば、Rivier et al., J. Med. Chem. 12:42:3175-82 (1999)を参照のこと)。これら知見は、上記低分子NB1-77860(化合物1)で再現された。副腎摘出ラットにおいて、化合物1は、ACTH低下に関する強力な能力を有する。ACTHにおける最大の低減は、NB1-77860のピーク血漿濃度と相関した；しかし、ACTH低下効果の持続時間は、薬物血漿曝露を超えていた。従って、副腎摘出ラットにおいて、NB1-77860の統合された血漿曝露と経口投与後のインビボ効力との間に推定可能な関係が存在する。

【0057】

CRFレセプターアンタゴニストとしての化合物の有効性は、種々のアッセイ法によって決定され得る。本明細書で記載されるCRFアンタゴニストは、CRFの、そのレセプターへの特異的結合を阻害し得、結果として、CRFに関連する活性を拮抗し得る。ある化合物は、1種以上の一般に受け入れられているアッセイ(実施例中に記載されるアッセイが挙げられる)によって、CRFアンタゴニストとしての活性について評価され得る。本明細書で記載される方法に有用なCRFアンタゴニストは、CRFレセプターに対する親和性を示す化合物を含む。

【0058】

理論に拘束されることは望まないが、CAHの処置において、CRFレセプターアンタゴニストは、下垂体副腎皮質刺激ホルモン生成細胞からのACTH放出を潜在的にブロックし(それによって、アンドロゲンの生成を低下させる)、コルチゾールの補充のためのより洗練された処置方法論を可能にする。動物およびヒトでの研究は、ACTH放出に対する化合物1(NB1-77860)の薬理学的効果を示した。処置効力をモニターする場合に内分泌学者が使用する標準的な生体マーカー評価は、このCRF₁レセプターアンタゴニストの効果をモニターするために使用され得る。17-OHP、アンドロステンジオン、テストステロン、コルチゾールおよびACTHの血漿レベル、ならびにこれらステロイドの尿代謝産物は、小児および成人の両方において容易に測定され、処置の影響に関する迅速かつ有意義なデータを与える。

(処置についての薬学的組成物および方法)

【0059】

本開示は、本明細書で記載されるCRFアンタゴニスト化合物のうちのいずれか1種および薬学的に受容可能な賦形剤を含む、CAHを処置するための方法において使用するための薬学的組成物をさらに提供する。薬学的に受容可能な賦形剤は、活性成分の活性に干渉しない、生理学的におよび薬学的に適した、非毒性でかつ不活性な物質もしくは成分である；賦形剤はまた、キャリアともいわれ得る。上記CRFアンタゴニスト化合物は、処置もしくは防止的(もしくは予防的)処置(例えば、CAH疾患の増悪、または上記疾患の1以上の症状の発生もしくは再発を低減する)において使用するための薬学的組成物に製剤化され得る。本明細書で記載される方法および賦形剤は例示であり、決して限定ではない。薬学的に受容可能な賦形剤は、薬学分野において周知であり、例えば、Rowe et al., Handbook of Pharmaceutical Excipients: A Comprehensive Guide to Uses, Properties, and Safety, 5th Ed., 2006, および

Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005))に記載される。薬学的に受容可能な賦形剤の例としては、滅菌生理食塩水および生理学的 pH のリン酸緩衝化生理食塩水が挙げられる。保存剤、安定化剤、色素、緩衝化剤などは、上記薬学的組成物の中に提供され得る。さらに、抗酸化剤および懸濁剤もまた、使用され得る。

【0060】

治療的および／もしくは予防的利益としては、例えば、改善された臨床転帰（治療的処置および予防的もしくは防止の手段の両方）が挙げられ、ここでその目的は、望ましくない生理学的変化もしくは障害を防止するもしくは遅らせるもしくは遅延させる（減らす）こと、またはこのような障害の拡大もしくは重篤度を防止するもしくは遅らせるもしくは遅延させる（減らす）ことである。本明細書で考察される場合、被験体を処置することからの有益なもしくは望ましい臨床結果としては、以下が挙げられるが、これらに限定されない：処置される予定の疾患、状態もしくは障害から生じるかもしくはこれらに関連する症状の減退、減少、もしくは緩和；症状の発生の減少；クオリティ・オブ・ライフの改善；疾患がない状態（すなわち、被験体が症状（これに基づいて、疾患の診断が行われる）を示す見込みもしくは傾向を減少させること）が長くなる；疾患の程度の縮小；疾患の安定した（すなわち、悪化していない）状態；疾患進行の遅滞もしくは遅れ；上記疾患状態の改善もしくは軽減；ならびに検出可能であろうと検出不能であろうと、退縮（部分的であろうが全体であろうが）；ならびに／または全生存。「Treatment（処置）」はまた、被験体が処置を受けなかった場合に予測される生存と比較したときに、生存を長期化することを意味し得る。処置の必要性のある被験体としては、上記状態もしくは障害を既に有している人々、ならびに上記疾患、状態もしくは障害を有する傾向にあるかまたは発生させるリスクのある被験体、ならびに上記疾患、状態もしくは障害が防止される（すなわち、上記疾患、障害もしくは状態の発生の見込みを減少させる）べきである人々が挙げられる。被験体は、ヒトもしくは非ヒト哺乳動物（例えば、ラット、マウス、イヌ、ネコ、家畜、動物園動物）であり得る。

【0061】

至適用量は、一般に、実験モデルおよび／もしくは臨床試験を使用して決定され得る。上記至適用量は、上記被験体のボディーマス、体重、もしくは血液容積に依存し得る。一般に、ある用量の中に存在する、本明細書で記載される化合物の量は、約 0.1 mg ～ 約 30 mg / kg 被験体体重の範囲に及ぶ。ある種の実施形態において、単一用量は、約 50 ～ 1000 mg である。有効な治療を提供するために十分である最少用量の使用は、通常好ましい。被験体は、一般に、臨床評価によって、および処置もしくは防止されている状態に適したアッセイを使用して、治療有効性についてモニターされ得る。このアッセイは、当業者が精通しており、本明細書に記載される。被験体に投与される化合物のレベルは、生物学的流体中の、例えば、血液、血液画分（例えば、血清）および／もしくは尿中の、ならびに／または上記被験体に由来する他の生物学的サンプル中の上記化合物のレベルを決定することによってモニターされ得る。上記化合物を検出するために当該分野で実施される任意の方法は、治療レジメンの経過の中で化合物のレベルを測定するために使用され得る。

【0062】

本明細書で記載される化合物のうちの少なくとも1種を含む、CAHまたは関連疾患もしくは障害を処置するための組成物の用量は、上記被験体の状態、すなわち、上記疾患のステージ、上記疾患によって引き起こされる症状の重篤度、全身の健康状態、ならびに年齢、性別および体重、ならびに医療分野の当業者に明らかな他の因子に依存し得る。同様に、上記化合物の用量は、医療分野の当業者によって理解されるパラメーターに従って決定され得る。

【0063】

本明細書で記載されるCRF₁アンタゴニスト化合物のうちの少なくとも1種を含む本

明細書で記載される薬学的組成物は、上記化合物の有効量を効率的に送達するいくつかの経路のうちのいずれか1つによって、必要性のある被験体に投与され得る。このような投与経路としては、例えば、経口、非経口、腸、直腸、鼻内、口内、舌下、筋肉内、および経皮が挙げられる。これら投与経路などによって投与される組成物は、本明細書でより詳細に記載される。

【0064】

開示される化合物もしくは組成物の投与は、夜間投与もしくは寝る前の投与（すなわち、就寝時投与）を含む。本明細書で使用される場合、就寝時投与とは、予測される概日リズムによるACTH放出の時にもしくはその前に（例えば、2～5時間前）、上記CRF₁アンタゴニストの臨床的に関連する濃度を送達するように意図された投与をいう。このACTH放出は、代表的には午前1～2時であるので、そして大部分の経口投与された薬物は数時間というT_{max}を有するので、例えば、予測される概日リズムによるACTH放出の3～4時間前である午後10時の投与は、望ましい。この同じプレパルス就寝時投与は、シフト労働者（例えば、夜間に働いて日中に睡眠をとる人々）のために適合させられ得、この場合には、投与は、必ずしも夜間に起こらなくてもよい。従って、投与は、予測される概日リズムによるACTH放出に依存し、個体の（すなわち、被験体、患者の）特定の労働および睡眠パターンに依存して変動し得る。ある種の実施形態において、本明細書で記載されるCRF₁レセプターアンタゴニスト（例えば、NBI-77860、またはNBI-30775、NBI-34041、SSR-126374、SSR-125543、アンタラルミン（N-ブチル-N-エチル-2, 5, 6-トリメチル-7-（2, 4, 6-トリメチルフェニル）ピロロ[3, 2-e]ピリミジン-4-アミン）、もしくはDMP904のうちのいずれか1種）は、予測される概日リズムによるACTH放出前（すなわち、先に、先だって）の約2～5時間の間に投与される。他の実施形態において、上記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出前の約2～4時間の間もしくは3～5時間の間に、上記被験体に投与される。より具体的な実施形態において、CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出前の約3～4時間の間に上記被験体に投与される。

【0065】

CAHを有する被験体（すなわち、患者、個体）における17-OHPおよび／もしくはACTHレベルを、CRF₁レセプターアンタゴニストを投与する工程によって低下させるための方法もまた、本明細書で提供される。ある種の実施形態において、上記アンタゴニストは、予測される概日リズムによるACTH放出の時にもしくはその前に投与される。他のある種の実施形態において、上記CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の前の約2～4時間の間もしくは約3～5時間の間に投与される。より具体的な実施形態において、CRF₁レセプターアンタゴニストは、予測される概日リズムによるACTH放出の前の約3～4時間の間に上記被験体に投与される。

【0066】

CRF₁レセプターアンタゴニストを必要性のある女性被験体に、上記被験体においてACTHおよび17-OHPのレベルの低下を引き起こす本明細書で記載される様式で投与する工程を包含する本明細書で記載される方法は、アンドロゲン（例えば、テストステロンおよびアンドロステジオンの放出の低下を生じ得る。グルココルチコイドの用量は、臨床的に有意な量によって付随して低下させられ得、これは、翻って副作用の低下を生じる。

【0067】

CAHを有する患者および若く成長中である患者における維持療法のための、ならびに成熟した患者における維持療法のためのグルココルチコイド（GC）および鉱質コルチコイド（MC）の量は、当業者に公知である。例えば、ガイドラインは、Speiser et al. (J. Clin. Endocrinol. Metab. 95:4133-60 (2010)（その全体において参考として援用される）に記載され、そ

の中の表1および表2に示される。特に、CAHを有する若く成長中である患者に関しては、当業者は、GCでの高すぎる投与が上記患者において身長成長 (s t a t u r a l growth) を妨げ得ることを認識する。よって、CRF₁レセプターアンタゴニストで患者を処置するための本明細書で記載される方法は、臨床的に有意な様式でGCの用量を低下させる工程を包含し得る。

【0068】

ある種の実施形態において、CRF₁レセプターアンタゴニストを投与する工程によってCAHを処置するための方法は、CAHを有する被験体を処置するために現在推奨されるGC用量より低い用量で、GCを投与する工程をさらに包含し得る。上記被験体が成熟した患者である場合、GCの用量 (例えば、成熟した被験体における維持療法のために推奨されるヒドロコルチゾン (HC)、プレドニゾン、プレドニゾロン、デキサメタゾン、もしくはフルドロコルチゾンの用量) は、15~25 mg/日 HC; 5~7.5 mg/日 プレドニゾン、4~6 mg/日 プレドニゾロン; 0.25~0.5 mg/日 デキサメタゾン、もしくは0.05~0.2 mg/日 フルドロコルチゾンという推奨用量から、約10%、15%、20%、30%、40%、50%、60%以上の程度、低下させられ得る。CAHを有する成長中である被験体において、GC (例えば、HC) の推奨用量は、10~15 mg/m²/日という合計推奨用量から低下させられ得、そして/または0.05~0.2 mg/日のフルドロコルチゾンという合計用量は、各々、本明細書で記載されるとおりのCRF₁レセプターアンタゴニストを受ける被験体において約10%、15%、20%、30%、40%、50%、60%以上の程度低下させられ得る。一実施形態において、必要性のある被験体に有効量のCRF₁アンタゴニストを投与する工程を包含する本明細書で記載される方法は、プラセボと比較して、ACTHレベルの臨床的に有意な低下を生じる。具体的実施形態において、必要性のある被験体に有効量のCRF₁アンタゴニストを投与する工程は、プラセボと比較して、ACTHレベルの臨床的に有意な低下を生じ、ここでその低下は、少なくとも25%である。別の実施形態において、必要性のある被験体に有効量のCRF₁アンタゴニストを投与する工程は、プラセボと比較して、ACTHレベルの臨床的に有意な低下を生じ、ここでその低下は、少なくとも50%である。グルココルチコイドおよび鉱質コルチコイドの投与に関するガイドラインについては、Speiser et al. (前出) を参照のこと。

【0069】

別の実施形態において、必要性のある被験体に有効量のCRF₁アンタゴニストを投与する工程を包含する本明細書で記載される方法は、プラセボと比較して、17-OHPレベルの臨床的に有意な低下を生じる。別の具体的実施形態において、必要性のある被験体に有効量のCRF₁アンタゴニストを投与する工程は、プラセボと比較して、17-OHPレベルの臨床的に有意な低下を生じ、ここでその低下は、少なくとも25%である。さらに別の実施形態において、必要性のある被験体に有効量のCRF₁アンタゴニストを投与する工程は、プラセボと比較して、17-OHPレベルの臨床的に有意な低下を生じ、ここでその低下は、少なくとも50%である。

【0070】

一実施形態において、必要性のある被験体に有効量のCRF₁アンタゴニストを投与する工程を包含する本明細書で記載される方法は、プラセボと比較して、ACTHレベルおよび17-OHPレベルの両方の臨床的に有意な低下を生じる。ある種の実施形態において、必要性のある被験体に有効量のCRF₁アンタゴニストを投与する工程は、プラセボと比較して、ACTHレベルおよび17-OHPレベルの両方の臨床的に有意な低下を生じ、ここで上記低下は、少なくとも25%である。別の具体的実施形態において、必要性のある被験体に有効量のCRF₁アンタゴニストを投与する工程は、プラセボと比較して、ACTHレベルおよび17-OHPレベルの両方の臨床的に有意な低下を生じ、ここで上記低下は、少なくとも50%である。

【0071】

上記薬学的組成物は、液剤の形態にあり得る。あるいは、それらは、固体 (例えば、散

剤、錠剤など)の形態にあり得る。本明細書で記載される化合物のうちのいずれか1種を含む組成物は、徐放性もしくは緩慢な放出のために製剤化され得る。このような組成物は、一般に、周知の技術を使用して調製され得、例えば、経口、直腸もしくは皮下移植によって、または所望の標的部位での移植によって、投与され得る。徐放性製剤は、キャリアマトリクスの中に分散された、および/もしくは速度制御膜によって囲まれたレザバ内に含まれた化合物を含み得る。このような製剤内で使用するための賦形剤は、生体適合性であり、生分解性でもあり得る；好ましくは、上記製剤は、活性成分放出の比較的一定なレベルを提供する。徐放性製剤内に含まれる活性化合物の量は、移植部位、放出の速度および予測される持続時間、ならびに処置もしくは防止される予定の状態の性質に依存する。

【0072】

経口製剤に関しては、本明細書で記載される化合物のうちの少なくとも1種は、単独で使用されるかまたは適切な添加剤と併用されて、例えば、従来の添加剤(例えば、ラクトース、マンニトール、コーンスターチもしくはジャガイモデンプン)とともに；結合剤とともに；崩壊剤とともに；滑沢剤とともに；および望ましい場合には、希釈剤、緩衝化剤、湿潤剤、保存剤、着色剤、および矯味矯臭剤とともに、錠剤、散剤、粒剤もしくはカプセル剤を作製し得る。上記化合物は、胃の環境の低pHからの上記化合物の保護を提供するための緩衝化剤および/もしくは腸溶性コーティングとともに製剤化され得る。上記組成物に含まれる化合物は、例えば、液体、固体もしくは半固体の製剤の中で矯味矯臭剤とともに、および/または腸溶性コーティングとともに、経口送達のために製剤化され得る。経口製剤は、粉末化キャリア(例えば、ラクトース、デンプン、セルロース誘導体、ステアリン酸マグネシウム、ステアリン酸など)とともに上記活性化合物を含み得るゼラチンカプセルとして提供され得る。類似のキャリアおよび希釈剤は、圧縮された錠剤を作製するために使用され得る。

【実施例】

【0073】

実施例1：CRFレセプター結合活性

本明細書で記載される方法において使用されるとおりのCRFアンタゴニストは、Grigoriadis et al. (例えば、Mol. Pharmacol vol 50, pp 679-686, 1996を参照のこと)およびHoare et al. (例えば、Mol. Pharmacol 63: 751-765, 2003を参照のこと)によって一般に記載されるとおりの標準的放射性リガンド結合アッセイによって、上記CRFレセプターへの結合活性について評価され得る。放射性標識したCRFリガンドを利用することによって、上記アッセイは、本明細書で記載される化合物と任意のCRFレセプターサブタイプとの結合活性を評価するために使用され得る。

【0074】

簡潔には、上記結合アッセイは、放射性標識したCRFリガンドを上記CRFレセプターから置き換えることを包含する。より具体的には、上記結合アッセイは、ヒトCRFレセプターで安定してトランスフェクトされた細胞に由来する1~10 μ g 細胞膜を使用して、96ウェルアッセイプレートの中で行われる。各ウェルは、目的の化合物もしくは参照リガンド(例えば、ソバジン、ウロコルチンI、もしくはCRF)、0.05 mLの $[^{125}\text{I}]$ チロシン-ソバジン(終濃度約150 pMもしくはスキッチャード分析によって決定される場合のほぼ K_D)および上記CRFレセプターを含む細胞膜懸濁物0.1 mLを含む、約0.05 mL アッセイ緩衝液(例えば、ダルベッコのリン酸緩衝化生理食塩水、10 mM 塩酸マグネシウム、2 mM EGTA)を受容する。上記混合物を、2時間、22℃でインキュベートし、続いて、ガラス繊維フィルタでの迅速濾過によって、結合した放射性リガンドと遊離の放射性リガンドとを分離する。3回洗浄した後、上記フィルタを乾燥させ、放射活性(^{125}I のオージェ電子)を、シンチレーションカウンターを使用して計数する。全ての放射性リガンド結合データを、非線形最小二乗曲線フィッティングプログラムPrism(GraphPad Software Inc)もしくはXLfit(ID Business Solutions Ltd)を使

用して分析し得る。

実施例2：CRF₁レセプターアゴニスト活性

【0075】

Fleck et al. (J. Pharmacology and Experimental Therapeutics, 341(2):518-531, 2012) (本明細書中以降「Fleck et al.」, その全体において参考として援用される)に報告されるように、以前同定されたCRF₁レセプターアンタゴニストの活性が示される。このような活性は、以下の式によって、会合速度定数(k_1)および解離速度定数(k_{-1})から計算される、速度論的に導出される親和性(K_i)として報告される:

$$K_i = k_{-1} / k_1$$

【0076】

また、Fleck et al. で報告されるように、以下の表1に列挙される上記CRF₁レセプターアンタゴニストの速度論的 K_i が報告された:

【表1-1】

表1
代表的CRF₁レセプターアンタゴニスト

リガンド	k_1 (10 ⁶ M ⁻¹ 分 ⁻¹)	速度論的 K_i (nM)
NBI-27914	9.4 ± 3	25

【表1-2】

リガンド	k_1 (10 ⁶ M ⁻¹ 分 ⁻¹)	速度論的 K_i (nM)
CP-316,311	13 ± 2	12
NBI-46200	6.2 ± 2	22
DMP696	7.7 ± 2	9.5
ペキサセルホント	2.6 ± 0.1	19
NBI-35965	20 ± 2	2.3
ONO-2333Ms	4.4 ± 2.2	15
アンタラルミン	3.4 ± 0.6	3.9
NBI-34041	8.3 ± 2.0	1.7
DMP904	18 ± 1	0.38
NBI-30775	14 ± 2.0	0.36
SSR125543A	33 ± 5	0.049

【0077】

この同じ技術によって、化合物 I (NBI-77860) の速度論的 K_i は、以下のとおりであることが見出された：

【表 1-3】

表 1(続き)

リガンド	k_i ($10^6 M^{-1} \text{分}^{-1}$)	速度論的 K_i (nM)
NBI-77860	0.24 ± 0.05	48 ± 9

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実施例 3：CRF₁ レセプターアンタゴニストの解離半減期 ($t_{1/2}$)

【0078】

本明細書で記載される方法において使用されるとおりの CRF₁ レセプターアンタゴニストの解離半減期 ($t_{1/2}$) を、Fleck et al. に記載される技術によって評価する。その中で記載されるように、標識されたおよび標識されていないリガンドに関する解離速度定数は、 k_{-1} と表される一方で、上記レセプターの薬物解離の半減期 ($t_{1/2}$) (これは、滞留時間中央値 (median residence time) に等しい) は、以下の式によって、解離速度定数 (k_{-1}) から計算される：

$$t_{1/2} = 0.693 / k_{-1}$$

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【0079】

Fleck et al. において報告されるように、以下の表 2 に列挙される CRF₁ レセプターアンタゴニストの解離半減期 ($t_{1/2}$) が報告された。

【表 2-1】

表2
代表的化合物の解離半減期

リガンド	k_{-1} (分 ⁻¹)	解離 $t_{1/2}$ (分)	
NBI 27914	0.27 ± 0.07	2.6	
CP-316,311	0.17 ± 0.04	4.1	10
NBI-46200	0.13 ± 0.002	5.3	
DMP696	0.095 ± 0.02	7.3	
ベキサセルホント	0.049 ± 0.001	14	
NBI-35965	0.048 ± 0.005	16	
ONO-2333Ms	0.063 ± 0.029	17	20
アンタラルミン	0.013 ± 0.002	53	
NBI-34041	0.013 ± 0.002	53	
DMP904	0.0072 ± 0.002	96	
NBI-30775	0.0054 ± 0.0006	130	
SSR125543A	0.0016 ± 0.0003	430	30

【0080】

この同じ技術によって、化合物 I (NBI-77860) の解離半減期は、以下のとおりであることが見出された：

【表 2-2】

表2(続き)

リガンド	k_{-1} 分 ⁻¹	解離 $t_{1/2}$ 分	
NBI-77860	0.012 ± 0.0003	58	40

【0081】

よって、30分間を超える解離半減期 ($t_{1/2}$) を有する CRF₁ レセプターアンタゴニストとしては、アンタラルミン、NBI-34041、DMP904、NBI-30775、SSR125543A、および NBI-77860 (化合物 I) が挙げられる (が、これらに限定されない)。これら同じ化合物はまた、40分間を超える解離半減期 ($t_{1/2}$) および 50分間を超える解離半減期 ($t_{1/2}$) を有する CRF₁ レセプター

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アンタゴニストの代表である。

実施例4：副腎摘出ラットにおけるACTHの低下

【0082】

化合物I (NBI-77860) (例えば、Tellew et al., Bloodrg. Med. Chem. Lett. 2010, 20:7259; WO2006044958を参照のこと)は、結合 pK_i 8.2、速度論的 K_i 49 nM (上記の表1)、および解離 $t_{1/2}$ 58分 (上記の表2)を有する強力なCRF₁アンタゴニストである。

【0083】

ペプチドCRF₁レセプターアンタゴニストの静脈内注射は、副腎摘出 (ADX) ラットにおいて高い血漿ACTHレベルを低下させることが示された (例えば、Rivier et al., J. Med. Chem. 12:42:3175-82 (1999)を参照のこと)。これら知見は、上記低分子NBI-77860で再現された。ADXラット ($n=6$ /群)に経口投与された場合、NBI-77860の30 mg/kg単一用量は、最大5時間にわたって血漿ACTHレベルを有意に低下させた (図2を参照のこと)。効力の持続時間は、薬物血漿曝露を超える時間経過とともに、ピーク血漿濃度と相関した。副腎摘出ラットにおいて、NBI-77860の統合された血漿曝露 (integrated plasma exposure) と経口投与後のインビボ効力との間には、推定可能な関係が存在する。

【0084】

Fleck et al. はまた、副腎摘出ラットにおける血漿ACTHレベルに対する、それらの解離半減期によって区別されるCRF₁レセプターアンタゴニスト；すなわち、NBI-30775、NBI-34041およびNBI-35965の効果を報告する。最高用量 (10 mg/kg) では、3種全てのリガンドがACTHを急激に低下させた (注射後1時間、図3A~C)。より長い持続時間の後、明らかな差異が、NBI-35965と他の2種のリガンドとの間に出てきた。上記ACTHレベルは、NBI-35965に関しては2時間までにビヒクルレベルへと戻った (図3C) のに対して、その応答は、NBI-30775およびNBI-34041に関しては、4~6時間にわたって持続した (図3Aおよび図3B)。

実施例5：ヒトにおける化合物Iの薬力学的効果

【0085】

この研究において、ヒト被験体に対するNBI-77860 (化合物I) の薬力学的効果を、プラセボおよび単一用量のアルプラゾラム (0.75 mg) に関して、メチラポン (0.04 g/kg) によって生成されるHPA系応答に対する単一経口用量の効果を観察することによって評価した。メチラポンは、副腎におけるコルチゾール合成をブロックし (それによって、CAHのコルチゾール欠損を模倣する)、ACTHレベルの急激な反射上昇と関連する。

【0086】

一次分析を、投与後30分~4時間の間のACTH値 (AUC (30分~4時間)) を決定することによって行った。この分析において、プラセボと比較して、以下の観察がなされた。ACTH AUC (30分~4時間) の有意な低下を、アルプラゾラムおよびNBI-77860、400 mg 処置で観察した。ACTH AUC (30分~4時間) の有意でない低下は、NBI-77860、50 mg 処置で認められた。AUC (30分~4時間) の増大は、NBI-77860、10 mg 処置で認められた。

【0087】

投与後2時間~4時間の間のACTH値 (AUC (2時間~4時間)) (曝露が C_{max} 値に達した場合の期間) に対して行った分析では、プラセボ処置期間と比較して、NBI-77860、400 mg および50 mg 処置期間においてACTHレベルが有意に低下した；しかし、上記低下は、10 mg 用量のNBI-77860では認められなかった。

実施例6：臨床研究

【0088】

この研究において、NBI-77860（化合物I）を、標題「先天性副腎皮質過形成を有する成人女性におけるNBI-77860の安全性および寛容性を評価するためのフェーズI、単盲検のプラセボ対照固定順単一用量研究（Phase I, Single-Blind, Placebo-Controlled, Fixed-Sequence, Single-Dose Study）」（IND 117, 388）という臨床研究において評価した。上記研究は、成人女性の古典的CAH患者における単盲検のプラセボ対照単一施設固定順単一用量臨床試験であった。これを、NBI-77860の安全性、寛容性、および血漿曝露、ならびにHPA系ホルモンの内因性レベルに対するこの化合物の効果を評価するためにデザインした。

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【0089】

古典的な21-ヒドロキシラーゼ欠損CAHと医学的に診断された合計8名の女性被験体（年齢19～58歳）に、3つの別個の処置期間の間に、NBI-77860 300 mg、600 mg、およびプラセボの単一就寝時用量（hs）を投与した（図4の研究デザイン模式図を参照のこと）。投与後16時間の血液サンプルが集められるまで（すなわち、約1400時間まで）、上記被験体の、同時のステロイド処置の通常の朝の用量を遅らせた。

【0090】

この研究に関するPDエンドポイントは、この患者集団における目的のHPA系生体マーカー；すなわち、17-ヒドロキシprogesteron（17-OHP；主要なPDエンドポイントとして）、副腎皮質刺激ホルモン（ACTH）、アンドロステジオン、テストステロン、および血清コルチゾールのレベルを含んだ。PD変数の初期分析は、各生体マーカーに関するグループ分けされた被験体データの調査であった（プラセボ条件と比較して、上記2種の活性物質（active）投与条件に関する投与前レベルからの平均%変化として表される）。投与後24時間の期間全体の平均17-OHPおよびACTHのレベルのデータを、図5に提供する。

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【0091】

17-OHPおよびACTHの両方の投与前レベルからの一貫したかつ臨床的に有意義な低下を、これらCAH患者において、プラセボと比較して、NBI-77860の投与後の投与後期間全体で観察した。群平均データに加えて、個々の応答を評価し、処置「応答者」を、朝のピーク期間の間にプラセボと比較して、活性なNBI-77860の下で17-OHPおよびACTHにおいて少なくとも50%低下を有するそれら被験体として控えめに定義した。この応答者分析から、上記研究において50%というかなり大きな応答者割合が得られた（これら患者のうちのいずれも、最初のプラセボ処置期間の間には応答者でなかった）。さらに、上記300 mg用量は、上記600 mg用量とほぼ同一の、17-OHPおよびACTHに対する効果を生じた。これら生体マーカーに関する個々の被験体の応答の例を、図6に提供する。

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【0092】

上記の種々の実施形態は、さらなる実施形態を提供するために組み合わせられ得る。本明細書中で言及されるおよび／または出願データシート中に列挙される全ての米国特許、米国特許出願公開、米国特許出願、外国特許、外国特許出願および非特許刊行物は、米国仮特許出願第61, 929, 941号（2014年1月21日出願）；同第61, 981, 033号（2014年4月17日出願）；および同第62/069, 155号（2014年10月27日出願）を含め、それらの全体において本明細書に参考として援用される。上記実施形態の局面は、上記種々の特許、出願および公開の概念を使用するために必要であれば、なおさらなる実施形態を提供するために改変され得る。

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【0093】

これらおよび他の変更は、上記の詳細な説明に鑑みて上記実施形態に対して行われ得る。一般に、以下の特許請求の範囲において、使用される用語は、特許請求の範囲を、本明

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細書および特許請求の範囲の中で開示される具体的実施形態に限定すると解釈されるものとするのではなく、均等物の全範囲（上記範囲に対して、このような特許請求項の範囲が権利付与される）とともに、全ての考えられる実施形態を含むと解釈されるものとする。よって、特許請求の範囲は、上記開示によって限定されない。

【図 1】

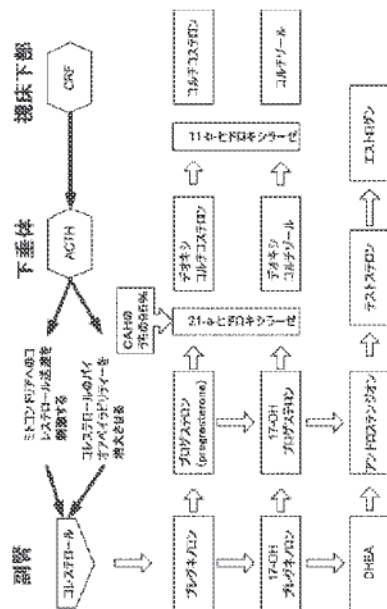


FIG. 1

【図 2】

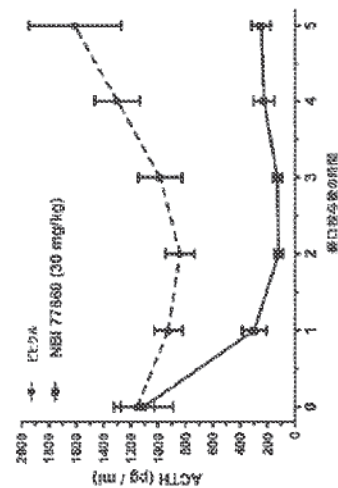
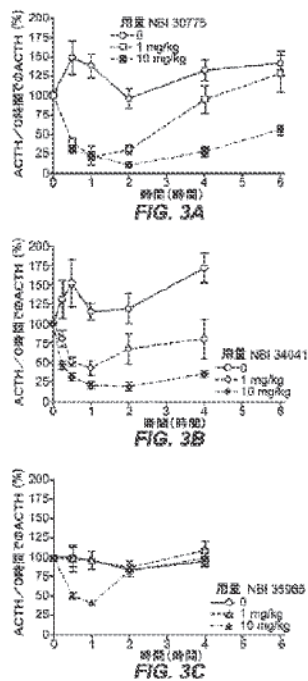


FIG. 2

【図 3】



【図 4】

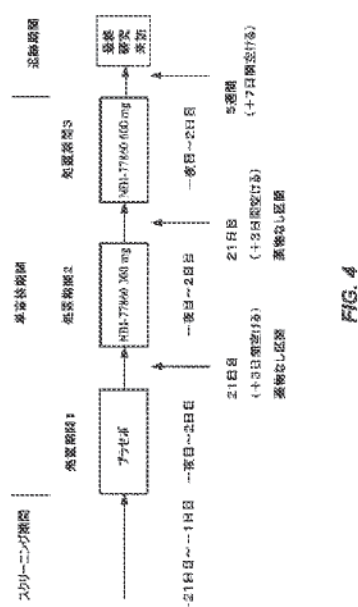


FIG. 4

【図 5】

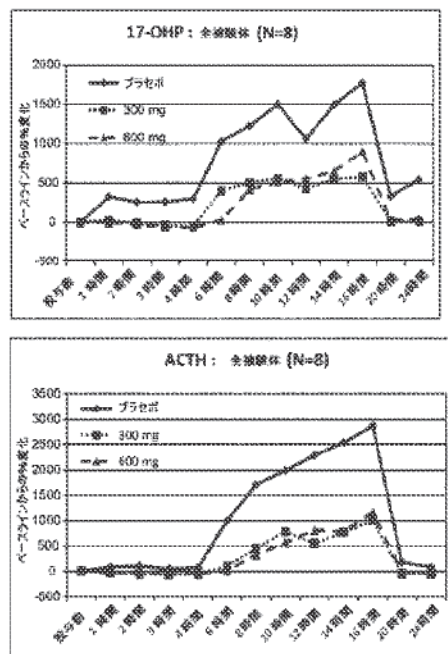


FIG. 5

【図 6】

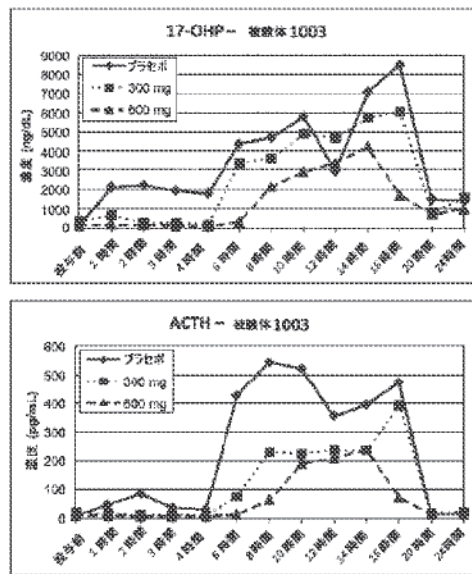


FIG. 6

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/012315

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/427 A61K31/4985 A61K31/519 ADD.		
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		
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) EPO-Internal, EMBASE, BIOSIS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category ^a	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim no.
X	US 8 030 304 B2 (CHEN ZHAOGEN [US] ET AL) 4 October 2011 (2011-10-04) cited in the application column 2, lines 13-46 column 2, line 56	1-3, 14-16
Y	----- ZOU MAKIS E ET AL: "Corticotropin-releasing hormone receptor antagonists", EUROPEAN JOURNAL OF ENDOCRINOLOGY, vol. 155, no. Suppl. 1, November 2006 (2006-11), pages S85-S91, XP002738177, ISSN: 0804-4643 page S86, left-hand column, paragraph 3; table 1	1-21
X	----- ZOU MAKIS E ET AL: "Corticotropin-releasing hormone receptor antagonists", EUROPEAN JOURNAL OF ENDOCRINOLOGY, vol. 155, no. Suppl. 1, November 2006 (2006-11), pages S85-S91, XP002738177, ISSN: 0804-4643 page S86, left-hand column, paragraph 3; table 1	1-3,5, 14-16,18
Y	----- -/-	1-21
☒ 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 "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 (see specification) "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 distinct or 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 "Z" document member of the same patent family		
Date of the actual completion of the international search 8 April 2015		Date of mailing of the international search report 21/04/2015
Name and mailing address of the ISA/ European Patent Office, P.O. Box 5618 Patentler 2 NL - 2280 HV Rijswijk Tel: (+31-70) 846-2040, Fax: (+31-70) 846-3079		Authorized officer Engl, Brigitte

Form PCT/ISA/210 (revised sheet) (April 2005)

page 1 of 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/012315

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	NEWFIELD ET AL: "ACTH receptor blockade: A novel approach to treat congenital adrenal hyperplasia, or Cushing's disease", MEDICAL HYPOTHESES, EDEN PRESS, PENRITH, US, vol. 74, no. 4, 1 April 2010 (2010-04-01), pages 705-706, XP026975604, ISSN: 0306-9877 [retrieved on 2010-03-18] the whole document -----	1-21
Y	JOHN E TELLEW ET AL: "Discovery of NBI-77860/GSK561679, a potent corticotropin-releasing factor (CRF) receptor antagonist with improved pharmacokinetic properties", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 20, no. 24, 19 October 2010 (2010-10-19), pages 7259-7264, XP028129093, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2010.10.095 [retrieved on 2010-10-24] cited in the application page 7264, left-hand column, lines 17-21 -----	1-21
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Form PCT/ISA/210 (continuation of second sheet) (April 2006)

page 2 of 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/012315

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WEBSTER E L ET AL: "In vivo and in vitro characterization of Antalarmin, a nonpeptide corticotropin releasing hormone (CRH) receptor antagonist: suppression of pituitary ACTH release and peripheral inflammation", ENDOCRINOLOGY, THE ENDOCRINE SOCIETY, US, vol. 137, no. 12, 1 January 1996 (1996-01-01), pages 5747-5750, XP000651739, ISSN: 0013-7227, DOI: 10.1210/EN.137.12.5747 the whole document -----	1-21

Form PCT/ISA/210 (continuation of second sheet) (April 2006)

page 3 of 3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2015/012315

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Form PCT/ISA/210 (patent family annex) (April 2005)

フロントページの続き

(81)指定国 AP(BW, CH, CM, KE, LR, LS, MW, NZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), EA(AM, AZ, BY, KG, KZ, RU, TJ, TM), EP(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), OA(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG), 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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US

F ターム(参考) 4C086 AAO1 AA02 BC17 EC82 CB05 CB06 CB09 MA01 MA04 NA14
ZC08 ZC42



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A61K 31/415 (2006.01) *C07D 487/04* (2006.01)
A61K 31/425 (2006.01) *A61P 5/24* (2006.01)
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(21) International Application Number:

PCT/US2018/046760

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14 August 2018 (14.08.2018)

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(30) Priority Data:

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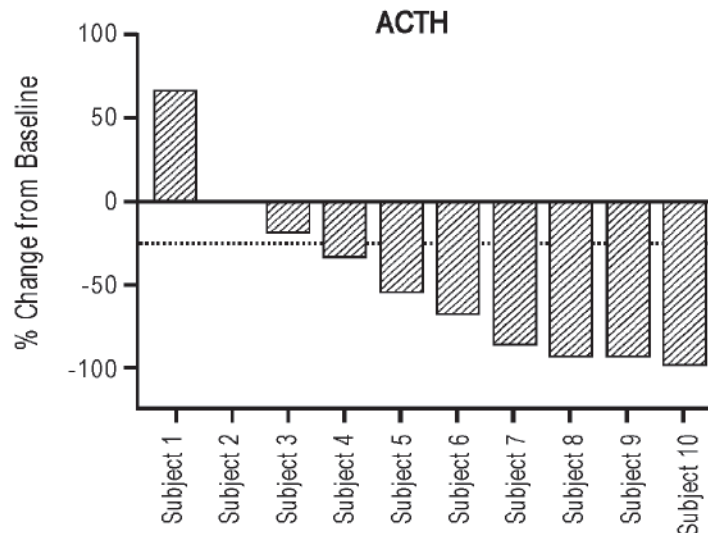
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 kind of national protection available*): AE, AG, AL, AM,
 AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
 CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
 DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
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 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, SM, ST, SV, SY, TH, TJ, TM, TN,
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(84) Designated States (*unless otherwise indicated, for every
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 GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
 UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
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 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: CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS

**FIG. 2**

(57) Abstract: The present invention provides novel pharmaceutical compositions comprising -(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine and methods of using the same for the treatment of Congenital adrenal hyperplasia (CAH).

[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))*

CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS**CROSS-REFERENCE**

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 62/545,406, filed August 14, 2017, which is incorporated herein by reference in its entirety.

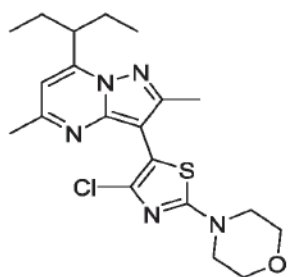
BACKGROUND OF THE INVENTION

[0002] 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 OF THE INVENTION

[0003] The present invention provides novel pharmaceutical compositions comprising 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine and methods using such pharmaceutical compositions for treating congenital adrenal hyperplasia (CAH).

[0004] In one aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

[0006] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm and about 20 μm . In some embodiments, the average size of the microparticles is between about 5 μm and about 15 μm . In some embodiments, the average size of the microparticles is less than about 10 μm .

[0007] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule. 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.

[0008] 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.

[0009] 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 pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition

comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0010] In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0011] In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 2 to about 6 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 3 to about 5 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 6 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 5 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 4 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 3 hours in a subject.

[0012] 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 once a day. In some embodiments, the pharmaceutical composition is administered twice a day. In some embodiments, the pharmaceutical composition is administered three times a day.

[0013] In some embodiments, the method further comprises administering a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount. In some embodiments, the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.

[0014] In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are reduced. In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.

[0015] In some embodiments, the glucocorticoid is hydrocortisone. In some embodiments, the hydrocortisone is administered at a dose less than about 15 mg/day. In some embodiments, the hydrocortisone is administered at a dose less than about 10 mg/day. In some embodiments, the hydrocortisone is administered at a dose less than about 5 mg/day.

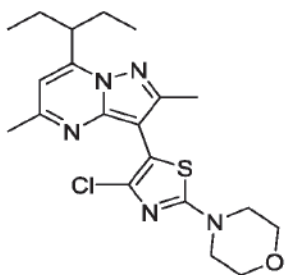
[0016] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 8 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 2 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 30 minutes.

[0017] In some embodiments, the method further comprises administering a mineralocorticoid. In some embodiments, the mineralocorticoid is fludrocortisone.

[0018] 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 mins 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 pharmaceutical composition is administered at or before the expected circadian release of adrenocorticotrophic hormone (ACTH). In some embodiments, the pharmaceutical composition is administered about 3-4 hours before the expected circadian release of adrenocorticotrophic hormone (ACTH). [0019] In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

[0020] In one aspect, the present disclosure provides 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 Compound 1:



or a pharmaceutically acceptable salt or solvate thereof; and

(iii) repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of compound 1.

[0021] In some embodiments, the hormone is 17 α -Hydroxyprogesterone (17-OHP), adrenocorticotrophic hormone (ACTH), testosterone, or androstenedione. In some embodiments, the hormone is 17-OHP, and the pre-determined range is from about 200 ng/dL to about 400 ng/dL. In some embodiments, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL. In some embodiments, the hormone is testosterone and the pre-determined range is from about 14 ng/dL to about 76 ng/dL. In some embodiments, the hormone is androstenedione and the pre-determined range is from about 30 ng/dL to about 150 ng/dL in males. In some embodiments, the hormone is androstenedione and the pre-determined range is from about 40 ng/dL to about 200 ng/dL in females.

[0022] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is

administered at a dose between about 200 mg/day and about 1000 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.

[0023] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 600 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and 400 mg /day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between 50 mg/day and 200 mg/day. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 50 mg /day.

[0024] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm and about 20 μm . In some embodiments, the average size of the microparticles is between about 5 μm and about 15 μm . In some embodiments, the average size of the microparticles is less than about 10 μm .

[0025] In some embodiments, Compound 1 is formulated in a pharmaceutical composition in the form of a capsule or a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule. 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.

[0026] 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.

[0027] In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0028] In some embodiments the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate

thereof. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0029] In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 2 to about 6 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 3 to about 5 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 6 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 5 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 4 hours in a subject. In some embodiments, the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 3 hours in a subject.

[0030] 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 once a day. In some embodiments, the pharmaceutical composition is administered twice a day. In some embodiments, the pharmaceutical composition is administered three times a day.

[0031] In some embodiments, the method further comprises administering a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount. In some embodiments, the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.

[0032] In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are reduced. In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the glucocorticoid is hydrocortisone.

[0033] In some embodiments, the hydrocortisone is administered at a dose less than about 15 mg/day. In some embodiments, the hydrocortisone is administered at a dose less than about 10 mg/day. In some embodiments, the hydrocortisone is administered at a dose less than about 5 mg/day.

[0034] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 8 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 2 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 30 minutes.

[0035] In some embodiments, the method further comprises administering a mineralocorticoid. In some embodiments, the mineralocorticoid is fludrocortisone.

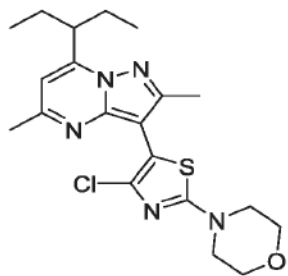
[0036] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at bedtime. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 4 hours before sleeping. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 2 hours before sleeping. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 30 mins before sleeping. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered in the evening. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at 10 pm at night.

[0037] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at or before the expected circadian release of adrenocorticotrophic hormone (ACTH). In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered about 3-4 hours before the expected circadian release of adrenocorticotrophic hormone (ACTH).

[0038] In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

[0039] In some embodiments, the subject in need thereof is from about 12 years of age to about 20 years of age.

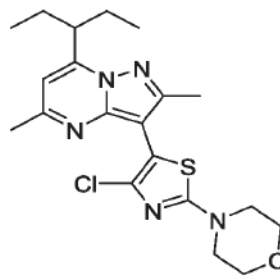
[0040] In one aspect, the present disclosure provides a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein

Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

[0041] In one aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a

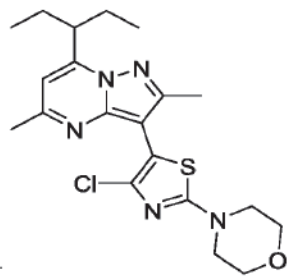


pharmaceutical composition comprising Compound 1:

; or a

pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

[0042] In one aspect, the present disclosure provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition

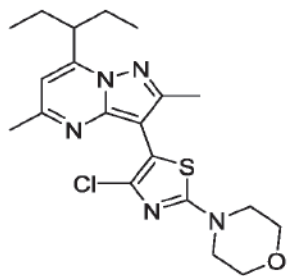


comprising Compound 1:

; or a pharmaceutically acceptable salt or

solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the metabolic symptoms are selected from the group consisting of body weight, BMI, waist circumference, blood pressure and glycemic control.

[0043] In one aspect, the present disclosure provides a method of improving quality of life in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day, wherein treatment results in an improved quality of life.

INCORPORATION BY REFERENCE

[0044] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] 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 of which:

[0046] **FIG. 1** shows Compound 1 in patients with CAH following 14-days of once daily dosing at each level;

[0047] **FIG. 2** demonstrates the attenuation of ACTH across different subjects due to the administration of Compound 1;

[0048] **FIG. 3** demonstrates the reduction in 17-OHP due to the administration of Compound 1;

[0049] **FIG. 4** demonstrates the reduction of Androstenedione due to the administration of Compound.

DETAILED DESCRIPTION OF THE INVENTION

[0050] 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.

[0051] 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. A more discrete septal/hypothalamic distribution and the availability of alternative endogenous ligands suggest a different functional role for the CRF2 receptor. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF 1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism. In other cases, CRF2 agonism produces similar effects to those reported for CRF 1 antagonists or CRF 1 gene deletion. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well.

[0052] 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. 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.

[0053] 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, testosterone, renin activity, and electrolytes.

[0054] Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, 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 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 increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients.

[0055] CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotrophic 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.

[0056] 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.

[0057] 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.

[0058] In one embodiment, the CRF receptor antagonist useful for the treatment of CAH is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine.

Certain Definitions

[0059] 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.

[0060] 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.

[0061] The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value.

[0062] 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.”

[0063] 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.

[0064] “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.

[0065] 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.

[0066] The term “pharmaceutical composition” means a composition comprising at least one active ingredient, such as Compound 1, 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.

[0067] The term “supraphysiologic” amount” describes hormones levels that are elevated compared to average levels found in healthy individuals.

[0068] The term “physiologic amount” describes average hormone levels found in healthy individuals.

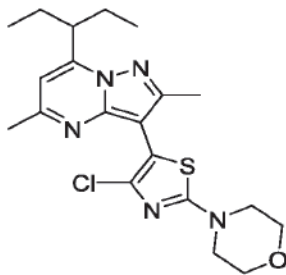
[0069] A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical 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. [0071] 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. 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 of the invention 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.

Compound

[0072] 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, and/or a solvate thereof:



. 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 1. 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 1.

Pharmaceutical Compositions

[0073] Disclosed herein is a pharmaceutical composition comprising Compound 1, a pharmaceutically acceptable salt, and/or a solvate thereof.

Dosage Form

[0074] 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 Compound 1 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.

[0075] 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.

[0076] 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

[0077] 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.

[0078] 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.

[0079] In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients. In some embodiments, the capsule is free of additional excipients.

[0080] 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

[0081] 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.

[0082] In some embodiments, the pharmaceutical composition is formulated as a tablet.

[0083] 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 Compound 1 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 Compound 1 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 Compound 1 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 Compound 1. 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.

[0084] 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, 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.

[0085] In some embodiments, the tablet is produced at a commercial scale.

[0086] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[0087] 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.

Pharmaceutically Acceptable Excipients

[0088] 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.

[0089] 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, glycol 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, α -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

[illegible]

In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 1 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule comprises about 5 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0091] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0092] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 20 mg and about 500 mg of Compound 1, or a

[illegible]

pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 30 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0094] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 40 mg and about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0095] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt

or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 90 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 50 mg and about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0096] In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 100 mg and about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0097] In some embodiments, the pharmaceutical composition comprises about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1, or a pharmaceutically

acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 70 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 40 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

Particle size

[0098] In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises Compound 1, or a pharmaceutically acceptable salt or solvate thereof, 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 50 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 5 μm to about 15 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 3 μm to about 10 μm . In some embodiments, microparticles of Compound 1 have an average size from about 4 μm to about 9 μm .

[0099] 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 80 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 .

Pharmacokinetics

[0100] In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 1 to about 8 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 2 to about 7 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 2 to about 6 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 3 to about 5 hours in a subject.

[0101] In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 8 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 7 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 6 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 5 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 4 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 3 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 2 hours in a subject. In some embodiments, Compound 1 is formulated as a capsule or a tablet as to provide a T_{max} of about 1 hour in a subject.

Stability

[0102] The pharmaceutical compositions described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to pharmaceutical compositions having about 95% or greater of the initial Compound 1 amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of Compound 1. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable pharmaceutical compositions have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable pharmaceutical compositions have about 5% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 4% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 3% w/w total impurities or related substances. In yet other embodiments, the stable pharmaceutical compositions have about 2% w/w total impurities or related substances. In yet

other embodiments, the stable pharmaceutical compositions have about 1% w/w total impurities or related substances.

[0103] At refrigerated condition, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5 ± 5 °C. In some embodiments, refrigerated condition is about 0 °C, about 0.1 °C, about 0.2 °C, about 0.3 °C, about 0.4 °C, about 0.5 °C, about 0.6 °C, about 0.7 °C, about 0.8 °C, about 0.9 °C, about 1 °C, about 1.1 °C, about 1.2 °C, about 1.3 °C, about 1.4 °C, about 1.5 °C, about 1.6 °C, about 1.7 °C, about 1.8 °C, about 1.9 °C, about 2 °C, about 2.1 °C, about 2.2 °C, about 2.3 °C, about 2.4 °C, about 2.5 °C, about 2.6 °C, about 2.7 °C, about 2.8 °C, about 2.9 °C, about 3 °C, about 3.1 °C, about 3.2 °C, about 3.3 °C, about 3.4 °C, about 3.5 °C, about 3.6 °C, about 3.7 °C, about 3.8 °C, about 3.9 °C, about 4 °C, about 4.1 °C, about 4.2 °C, about 4.3 °C, about 4.4 °C, about 4.5 °C, about 4.6 °C, about 4.7 °C, about 4.8 °C, about 4.9 °C, about 5 °C, about 5.1 °C, about 5.2 °C, about 5.3 °C, about 5.4 °C, about 5.5 °C, about 5.6 °C, about 5.7 °C, about 5.8 °C, about 5.9 °C, about 6 °C, about 6.1 °C, about 6.2 °C, about 6.3 °C, about 6.4 °C, about 6.5 °C, about 6.6 °C, about 6.7 °C, about 6.8 °C, about 6.9 °C, about 7 °C, about 7.1 °C, about 7.2 °C, about 7.3 °C, about 7.4 °C, about 7.5 °C, about 7.6 °C, about 7.7 °C, about 7.8 °C, about 7.9 °C, about 8 °C, about 8.1 °C, about 8.2 °C, about 8.3 °C, about 8.4 °C, about 8.5 °C, about 8.6 °C, about 8.7 °C, about 8.8 °C, about 8.9 °C, about 9 °C, about 9.1 °C, about 9.2 °C, about 9.3 °C, about 9.4 °C, about 9.5 °C, about 9.6 °C, about 9.7 °C, about 9.8 °C, about 9.9 °C, or about 10 °C. At accelerated conditions, the pharmaceutical compositions described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, or at least 24 month. Accelerated conditions for the pharmaceutical compositions described herein include temperatures that are at or above ambient levels (e.g. 25 ± 5 °C). In some instances, an accelerated condition is at about 40 ± 2 °C. In some instances, an accelerated condition is at about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C, or about 60 °C. Accelerated conditions for the pharmaceutical compositions described herein also include relative humidity (RH) that are at or above ambient levels ($55\pm 10\%$ RH). In other instances, an accelerated condition is above about 65% RH, about 70% RH, about 75% RH, or about 80% RH. In further instances, an accelerated condition is about 40 °C or 60 °C at ambient humidity. In yet further instances, an accelerated condition is about 40 ± 2 °C at $75\pm 5\%$ RH humidity.

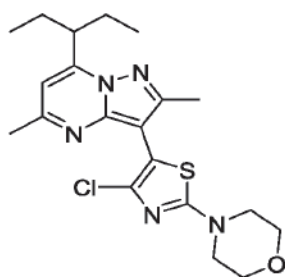
[0104] In some embodiments, the pharmaceutical compositions are stable at about 5 ± 5 °C to about 25 ± 5 °C for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5 ± 5 °C for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 25 ± 5 °C for at least 12 months. In one embodiment, the pharmaceutical compositions are stable at about 5 ± 5 °C for at least 24 months. In one embodiment, the pharmaceutical compositions are stable at about 25 ± 5 °C for at least 24 months.

Methods of Use

[0105] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH. 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, 17α -hydroxy pregnenolone, progesterone, 17α -hydroxy progesterone (17-OHP), dehydroepiandrosterone, androstenediol, androstenedione, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and adrenocorticotrophic hormone (ACTH). In some embodiments, the methods described herein result in the reduction of 17α -hydroxy progesterone (17-OHP). In some embodiments, the methods described herein result in the reduction of adrenocorticotrophic hormone (ACTH), also known as corticotropin.

[0106] Also disclosed herein 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 Compound 1:



or a pharmaceutically acceptable salt or solvate thereof;

- (iii) repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of compound 1.

[0107] In some embodiment, the hormone is 17α -Hydroxyprogesterone (17-OHP), adrenocorticotrophic hormone (ACTH), testosterone, or androstenedione.

[0108] In some embodiment, the hormone is 17-OHP, and the pre-determined range is from about 200 ng/dL to about 400 ng/dL. In some embodiment, the hormone is 17-OHP, and the pre-determined range is less than about 400 ng/dL, less than about 350 ng/dL, less than about 300 ng/dL, less than about 250 ng/dL, or less than about 200 ng/dL.

[0109] In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL. In some embodiment, the hormone is ACTH, and the pre-determined range is below about 100 pg/mL, below about 90 pg/mL, or below about 80 pg/mL.

[0110] In some embodiment, the hormone is testosterone and the pre-determined range is from about 14 ng/dL to about 76 ng/dL. In some embodiment, the hormone is testosterone and the pre-determined range is less than about 76 ng/dL, less than about 70 ng/dL, less than about 65 ng/dL, less than about 60 ng/dL, less than about 55 ng/dL, less than about 50 ng/dL, less than about 45 ng/dL, less than about 40 ng/dL, less than about 35 ng/dL, less than about 30 ng/dL, less than about 25 ng/dL, less than about 20 ng/dL, or less than about 15 ng/dL.

[0111] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 30 ng/dL to about 200 ng/dL in males. In some embodiment, the hormone is androstenedione and the pre-determined range is less than about 200 ng/dL, less than about 150 ng/dL, less than about 100 ng/dL, less than about 50 ng/dL, or less than about 30 ng/dL in males

[0112] In some embodiment, the hormone is androstenedione and the pre-determined range is from about 40 ng/dL to about 150 ng/dL in females. In some embodiment, the hormone is androstenedione and the pre-determined range is less about 150 ng/dL, less about 100 ng/dL, less about 50 ng/dL, or less about 40 ng/dL in females.

[0113] In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising Compound 1, 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 Compound 1, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer Compound 1, or a pharmaceutically acceptable salt or solvate thereof twice a day.

[0114] In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, Compound 1 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.

[0115] 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.

[0116] In some embodiments, about 100 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about

800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 600 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

[0117] In some embodiments, less than about 2000 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1200 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1000 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 800 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 600 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 500 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 400 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 300 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 200 mg Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered per day.

[0118] 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.

[0119] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

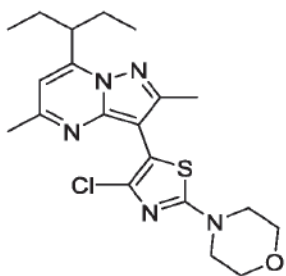
[0120] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 4 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than 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.

[0121] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

[0122] 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.

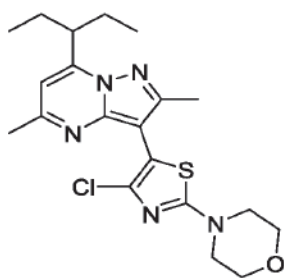
[0123] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at or before the expected circadian release of adrenocorticotrophic hormone (ACTH). In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein about 3-4 hours before the expected circadian release of adrenocorticotrophic hormone (ACTH). In some embodiments, the subject in need thereof is from about 12 years of age to about 20 years of age.

[0124] In one aspect, the present disclosure provides a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



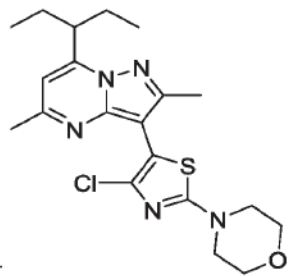
; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.

[0125] In one aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a



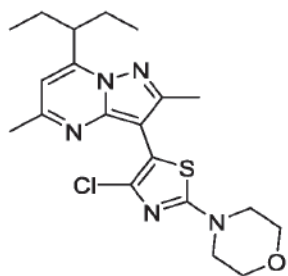
pharmaceutical composition comprising Compound 1: pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

[0126] In one aspect, the present disclosure provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition



comprising Compound 1: ; or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, the metabolic symptoms are selected from the group consisting of body weight, BMI, waist circumference, blood pressure and glycemic control.

[0127] In one aspect, the present disclosure provides a method of improving quality of life in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof, wherein

Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day, wherein treatment results in an improved quality of life.

Combination Therapy

[0128] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof; and a glucocorticoid. In some embodiments, the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0129] In some embodiments, the methods described herein reduce the amount of a glucocorticoid administered from a supraphysiologic amount to a physiologic amount.

[0130] In some embodiments, the methods described herein reduce the symptoms associated with high-dose glucocorticoid therapy. In some embodiments, the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis.

[0131] In some embodiments, the amount of glucocorticoid administered is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 80, or about 90% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the amount of glucocorticoid administered is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0132] In some embodiments, the amount of glucocorticoid administered is reduced by about 1% to about 90%, about 1% to about 60%, about 1% to about 30%, about 1% to about 10%, about 10% to about 50%, about 10% to about 40%, about 10% to about 30%, about 15% to about 25%, about 20% to about 30%, about 5% to about 25%, about 20% to about 50%, about

30% to about 60%, or about 40% to about 70% as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

[0133] In some embodiments, the glucocorticoid is administered at a dose between about 0.1 mg/day and about 25 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 20 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 15 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 12 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 9 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 8 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 7 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 6 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 5 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 4 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 3 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 1 mg/day and about 2 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 3 mg/day and about 13 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 8 mg/day and about 11 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 9 mg/day and about 12 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 9 mg/day and about 10 mg/day. In some embodiments, the glucocorticoid is administered at a dose between about 5 mg/day and about 10 mg/day.

[0134] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered in one pharmaceutical composition. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently in separate pharmaceutical compositions.

[0135] In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially. In some embodiments, Compound

1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 24 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 12 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 8 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 6 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 4 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 2 hours. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 1 hour. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 30 minutes. In some embodiments, Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered within 10 minutes.

[0136] In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the glucocorticoid is hydrocortisone.

[0137] In some embodiments, the glucocorticoid is hydrocortisone and the dose administered is less than the recommended dose of 15-25 mg/day.

[0138] In some embodiments, the glucocorticoid is prednisone and the dose administered is less than the recommended dose of 5-7.5 mg/day.

[0139] In some embodiments, the glucocorticoid is prednisolone and the dose administered is less than the recommended dose of 4-6 mg/day.

[0140] In some embodiments, the glucocorticoid is dexamethasone and the dose administered is less than the recommended dose of 0.25-0.5 mg/day.

[0141] Disclosed herein is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a combination of Compound 1, or a pharmaceutically acceptable salt or solvate thereof, a glucocorticoid; and optionally a mineralocorticoid. In some embodiments, the mineralocorticoid is fludrocortisone and the dose is less than the recommended dose of 0.05-0.2 mg/day.

EXAMPLES

[0142] 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.

[0143] 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: Pharmaceutical Composition

[0144] The pharmaceutical composition is manufactured as size 1 white hard gelatin capsules containing 200 mg of Compound 1 micronized to an average size of 10 microns or less. The pharmaceutical composition contains no additional excipients.

Example 2: Stability of the Pharmaceutical Composition

Stability Data Summary

[0145] A summary of the pharmaceutical composition stability studies is provided in Table 1. The pharmaceutical composition is a Compound 1 neat-filled into size 0 capsules with no added excipients, in 3 strength configurations: 1-mg, 5-mg, and 50-mg. The capsules were blister packaged in a polyvinyl chloride (PVC)-based film.

[0146] Under long term and accelerated conditions, no significant trend was observed in the three lots for any of the attributes evaluated throughout the course of the stability study.

Table 1. Summary of Stability

Lot Number	Strength	CCS	Stability Conditions	Available Data
#1	1-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#2	5-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#3	50-mg	PVC-based blister pack	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#4	200-mg	75 mL HDPE bottle	25 °C/60% RH	1 month
			40 °C/75% RH	9 months
#5	200-mg	30 mL HDPE bottle	25 °C/60% RH	6 months
			40 °C/75% RH	6 months
#6	200-mg	30 mL HDPE bottle	25 °C/60% RH	6 months
			40 °C/75% RH	6 months

CCS = container closure system; CRC = child-resistant closure; DoM = date of manufacture; HDPE = high density polyethylene; PVC = polyvinyl chloride

Stability Protocols

[0147] The stability protocol for various pharmaceutical compositions is provided in Table 2, 3, and 4.

Table 2. Stability Protocol

Test	Acceptance Criteria	Time (months)			
		T ₀	1	3	6
Appearance	Size 0 blue capsule containing yellow powder, blister pack and foil backing intact	X	A,B	A,B	A,B
Assay	Report (% Label Claim)	X	A,B	A,B	A,B
Related Substances	Report RRT and % each individual species and total	X	A,B	A,B	A,B
Disintegration	Report	X	A,B	A,B	A,B

RRT = relative retention time

X-testing performed at the time study was initiated

A-samples stored under long term conditions of 25 ± 2 °C/ 60 ± 5 % RH

B-samples stored under accelerated conditions of 40 ± 2 °C/ 75 ± 5 % RH

Table 3. Stability Protocol (200-mg capsules in 30 mL HDPE bottles)

Test	Acceptance Criteria	Time (months)			
		T ₀	1	3	6
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	A,B	A,B	A,B
Assay (%LC)	90.0 – 110.0	X	A,B	A,B	A,B
Related Substances					
Any Unspecified Impurity (%)	≤ 1.0	X	A,B	A,B	A,B
Total Impurities (%)	≤ 2.0				
Disintegration (min)	NMT 15	X	A,B	A,B	A,B
Water Activity	Report result	X	A,B	A,B	A,B

LC = label claim; NMT = not more than

X-testing performed at the time study was initiated

A-samples stored under long term conditions of $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$

B-samples stored under accelerated conditions of $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$

Table 4. *Stability Protocol (200-mg capsules in 30 mL HDPE bottles) for Lots to be Used in Phase 2 Clinical Study*

Test	Acceptance Criteria	Time (months)					
		T ₀	1	3	6	9	12
Appearance	Size 1 white capsule containing an off-white to yellow powder	X	B	A,B	A,B	A	A
Assay (%LC)	90.0 – 110.0	X	B	A,B	A,B	A	A
Related Substances Any Unspecified Impurity (%) Total Impurities (%)	≤ 1.0 ≤ 2.0	X	B	A,B	A,B	A	A
Disintegration (min)	NMT 15	X	B	A,B	A,B	A	A
Water Activity	Report result	X	n/a	n/a	n/a	A	A
Microbial Enumeration Total Aerobic Microbial Count (CFU/g) Total Combined Yeast and Mold (CFU/g) Count	NMT 2000 CFU/g NMT 200 CFU/g	X	n/a	n/a	n/a	A	A
Test for Specified Microorganisms <i>E. coli</i> (/g)	Absent	X	n/a	n/a	n/a	A	A

CFU = colony forming units; LC = label claim; n/a = not applicable; NMT = not more than

X-testing performed at the time study was initiated

A-samples stored under long term conditions of $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$

B-samples stored under accelerated conditions of $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$

[0148] The supportive data demonstrate that the pharmaceutical composition is stable for a minimum of 6 months (end of study). No adverse trends were observed under long term and accelerated conditions. The assay results were consistent through the entire study and no new related substances species were observed during the stability study. The reported stability results for lots stored in a blister packaging configuration are considered supportive for the updated packaging configuration of a 30-mL HDPE bottle, induction seal, and a child resistant

cap. There are no excipients in either configuration and both configurations provide protection from light.

Example 3: Phase 1 Clinical Studies

[0149] Compound 1 has been investigated in 2 Phase 1 studies in healthy adult volunteers.

[0150] Study 1 was the first-in-human study that investigated the safety, tolerability, and PK of single-escalating doses of Compound 1, given orally, to healthy adult subjects. Safety and tolerability assessments were made over a wide range of single oral doses, and dose escalation did not proceed until safety data from the preceding doses had been reviewed. The data from this study were used for the selection of doses for Study 2.

[0151] The 2-part multiple-dose study, Study 2, determined the safety and tolerability of repeated daily doses of Compound 1 and investigated the effects on biomarkers of relevance for the treatment of alcohol dependence. Part B investigated the interaction of Compound 1 with midazolam (a cytochrome P450 3A4 [CYP3A4] substrate), determining whether Compound 1 significantly inhibited the metabolism of drugs that are metabolized by CYP3A4.

[0152] In Study 1, Compound 1 was administered to healthy adult subjects as a single PO dose of 2, 10, 50, 150, 400, or 800 mg in the fed state and 150 mg in the fasted state. Absorption occurred moderately late, achieving peak C_{max} between 4 to 6 hours following dosing in the fed state.

[0153] Table 5 provides a summary of the PK parameters at each dose level. When Compound 1 was given in the fed state, median time to reach maximum plasma concentration (T_{max}) occurred between 4 and 6 hours. The median T_{max} was 10.05 hours when Compound 1 was given in the fasted state at 150 mg and ranged between 6 and 12 hours, suggesting possible delayed absorption in the fasted state. Mean half-life ($t_{1/2}$) after a single PO dose (fed and fasted state) was between 31 and 44 hours, ranging from 11 to 101 hours. Apparent volume of distribution (V_z/F) was large and appeared highly variable with greatest variability observed at the 2 highest dose levels of 400 mg and 800 mg.

Table 5. Summary of Pharmacokinetic Parameters of Compound 1 Following Single Oral Dose Administration in Healthy Volunteers (all Fed)

PK Parameters	Geometric Mean (CV%)					
	Analyte = Plasma Compound 1					
	2 mg	10 mg	50 mg	150 mg	400 mg	800 mg
N	6	6	6	6	6	6
C_{max} (ng/mL)	0.867 (53)	3.01 (87)	19.5 (39)	93.4 (22)	207 (92)	382 (110)
T_{max}^a (h)	6.00 (4.00-6.00)	4.00 (2.00 -6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	4.00 (3.00 - 6.00)	6.00 (4.00 - 6.00)
$t_{1/2}^b$ (h)	NC	NC	31	29.2	44.2	41.9

	(NC)	(NC)	(10.8-53.4)	(20.0 - 41.5)	(20.2 - 101)	(24.1 - 67.8)
AUC _{0-t_{last}} (ng•h/mL)	NC (NC)	NC (NC)	152 (60)	891 (26)	2300 (103)	4390 (100)
AUC _{0-∞} (ng•h/mL)	NC (NC)	NC (NC)	165 (64)	956 (25)	2580 (93)	4850 (95)
CL/F (L/h)	NC (NC)	NC (NC)	302 (64)	157 (25)	155 (93)	165 (95)
V _z /F (L)	NC (NC)	NC (NC)	13500 (45)	6620 (38)	9890 (212)	9970 (144)
V _{ss} /F (L)	NC (NC)	NC (NC)	8080 (36)	4600 (33)	6580 (152)	6820 (120)

AUC = area under the plasma concentration-time curve; CL/F = oral clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; NC = not calculable; t_{1/2} = elimination half-life; T_{max} = time to reach maximum plasma concentration; V_{ss}/F = volume of distribution at steady state; V_z/F = volume of distribution at terminal phase

a Median (range)

b Geometric mean (range)

[0154] As part of this single-dose escalation study, a food effect PK investigation was performed to examine Compound 1 exposures in both the fed and fasted states at the 150-mg dose level. A total of 6 subjects were administered 150 mg Compound 1 in each of these 2 dosing groups. Of these 6 subjects, 4 subjects received Compound 1 at the same dose in both fed and fasted states. The administration of Compound 1 in the fasted state resulted in a much flatter mean concentration-time (i.e., with significantly lower absorption) profile when compared against the mean profile at the same dose, given within 5 minutes after a standardized breakfast meal. The mean AUC_{0-∞}, and C_{max} values for a 150-mg dose in the fed state was approximately 3- and 11-fold greater than that of the fasted state, respectively. Table 6 provides a summary of the PK parameters at the 150-mg dose level under both fed and fasted state conditions.

Table 6. Summary of Pharmacokinetic Parameters of Compound 1 Following Single Oral Dose Administration in Healthy Volunteers – Fed vs. Fasted State

Pharmacokinetic Parameters	Geometric Mean (CV %)	
	Analyte = Plasma Compound 1	
	150 mg Fed	150 mg Fasted
N	6	6
C _{max} (ng/mL)	93.4 (22)	8.22 (83)
T _{max} ^a (h)	4.00 (3.00 – 6.00)	10.05 (6.00 – 12.00)
t _{1/2} ^b (h)	29.2 (20.0 – 41.5)	38.4 (24.2 – 88.5)
AUC _{0-t_{last}} (ng•h/mL)	891	288

	(26)	(48)
AUC _{0-∞} (ng•h/mL)	956 (25)	331 (44)
CL/F (L/h)	157 (25)	454 (44)
V _z /F (L)	6620 (38)	25100 (81)
V _{ss} /F (L)	4600 (33)	25200 (68)

AUC = area under the plasma concentration-time curve; CL/F = apparent total body clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; N = number of subjects; NC = not calculable; PK = pharmacokinetic; T_{max} = time to reach maximum plasma concentration; t_{1/2} = elimination half-life; V_{ss}F = apparent volume of distribution at steady state during the terminal phase after extravascular administration; V_z/F = apparent volume of distribution during the terminal phase after extravascular administration.

a Median (range)

b Geometric mean (range)

[0155] PK parameters AUC_{0-∞} and C_{max} were analyzed separately for dose proportionality for Compound 1 from 50 to 800 mg when administered in the fed state. The analysis results suggested that for every doubling of dose, AUC_{0-∞} can be expected to increase 1.74 times more than what would be expected under dose proportionality. C_{max} appeared more than dose proportional but the formal test was inconclusive as the 90% confidence interval were partially within the 0.8 – 1.25 interval. Dose proportionality across administered doses in the fed state could not be concluded on the basis of AUC_{0-∞} or C_{max}.

[0156] PK were also evaluated in the multiple-dose, dose-escalation study, Study 2. In Part A of the study, subjects were divided into 3 cohorts and received 50, 150, or 200 mg Compound 1 or placebo for 14 consecutive days (at least 6 subjects received Compound 1 and 2 subjects received placebo in each cohort). Blood concentrations of Compound 1 were close to steady-state levels after 2 weeks of dosing and the accumulation ratio was between 2.51 to 3.65. Part B investigated the interaction of Compound 1 with midazolam (a CYP3A4 substrate), thereby determining whether this compound significantly inhibited the metabolism of drugs that are metabolized by CYP3A4 serial blood samples were collected to determine plasma concentrations of study drug after a single dose of Compound 1 had been administered and at steady state. All dosing occurred in the fed state. An assessment of diurnal cortisol levels, plus when under conditions of glucose clamp, were also carried out both prior to and during the dosing period.

[0157] Overall concentration time profiles of Compound 1 showed that absorption was moderately delayed with $C_{\max}$ achieved at a median of 5 hours following oral dosing. Consistent with the single-dose study (Study 1), concentrations appeared to decline in a bi-exponential manner, characterized by a rapid decrease within the first 24 hours. Following multiple daily dosing for 2 weeks, the $t_{1/2}$ of Compound 1 exceeded 100 hours; therefore, an accumulation ratio of Compound 1 was between 2.51 to 3.65 (see Table 7). The $T_{\max}$ appeared to be consistent across doses. Overall half-lives, weight normalized CL/F and V/F were consistent for 150 and 200 mg. However, the values for these latter 2 parameters were almost doubled at the 50-mg dose level. Variability (CV%) for apparent clearance and volume of distribution were large and not reduced with weight-normalization.

Table 7. Summary of Noncompartmental Pharmacokinetic Parameters of Compound 1 After Single (Day 1) and Multiple (Day 14) Oral Doses of 50 mg, 150 mg, and 200 mg of Compound 1 in Part A of the Study

	Geometric Mean (CV%)					
	50 mg Day 1	150 mg Day 1	200 mg Day 1	50 mg Day 14	150 mg Day 14	200 mg Day 14
N	8	9	7	8	9	6
$C_{\max}$ (ng/mL)	22.7 (59)	127 (52)	143 (62)	50.3 (56)	222 (58)	314 (93)
$T_{\max}^a$ (hr)	4.52 (3.00 – 10.00)	5.00 (5.00 - 6.00)	5.00 (2.00 - 5.00)	5.00 (3.00 - 5.00)	5.00 (3.00 - 5.03)	5.00 (3.00 - 5.00)
Effective $t_{1/2}^b$ (hr)	NC NC	NC NC	NC NC	37.7 (27.4)	32.7 (29.7)	52.0
$AUC_{0-\infty}$ (ng•hr/mL)	NC NC	NC NC	NC NC	980 (53.8)	4680 (104)	5660 (122)
AUC_{0-24h} (ng•hr/mL)	97.6 (58)	590 (56)	559 (55 ^c)	273 (56)	1480 (66)	2040 (98)
C_{avg} (ng/mL)	NC NC	NC NC	NC NC	11.4 (56)	61.7 (66)	85.0 (98)
CL_{aa}/F (L/hr)	NC NC	NC NC	NC NC	183 (56)	101 (66)	98 (98)
WT-norm						
Cl_{aa}/F (L/hr/kg)	NC NC	NC NC	NC NC	2.88 (46.9)	1.42 (72.9)	1.50 (89.9)
V_z/F (L)	NC NC	NC NC	NC NC	33500 (90)	17600 (59)	16300 (76)
V_{ss}/F (L)	NC NC	NC NC	NC NC	12900 (91)	6170 (40)	5080 (78)
WT-norm						
V_{ss}/F (L/kg)	NC	NC	NC	204	86.5	77.4

	NC	NC	NC	(71.3)	(41.0)	(68.6)
	NC	NC	NC	2.80	2.51	3.65
R _A	NC	NC	NC	(27.4)	(29.7)	(34.4)

AUC = area under the plasma concentration-time curve; CL/F = apparent clearance; C_{max} = maximum plasma concentration; RA = accumulation ratio calculated as Day 14 AUC₀₋₂₄/Day 1 AUC₀₋₂₄; t_{1/2} = terminal half-life; effective t_{1/2} = half-life calculated by accumulation ratio; T_{max} = time to maximum plasma concentration; V_{ss}/F = volume of distribution at steady state; V_z/F = volume of distribution at terminal phase; WT-norm = weight normalized

^a Median (range).

^b Geometric mean (range).

^c n = 6, Dropout Subject 306 not included in the calculation of summary statistics.

[0158] Table 8 presents the results of the dose proportionality assessment for the AUC₀₋₂₄ and C_{max} over the tested dose range. For AUC₀₋₂₄ and C_{max}, the adjusted mean slope at Day 1 and Day 14 were all above the value of 1, suggesting a slightly more than proportional increase of AUC₀₋₂₄ and C_{max} values with increasing doses.

Table 8. Summary of Assessment of Dose Proportionality as Assessed by the Power Model for Plasma Compound 1

Parameter	Day	Mean Slope	Standard Error	90% CI for Slope	CV%
AUC ₀₋₂₄ (ng hr/mL)	1	1.40	0.194	(1.069, 1.737)	59.3
	14	1.48	0.221	(1.104, 1.864)	69.1
C _{max} (ng/mL)	1	1.41	0.185	(1.092, 1.728)	57.5
	14	1.33	0.210	(0.972, 1.693)	64.8

AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration

Safety

[0159] The safety of Compound 1 was evaluated in 2 Phase 1 studies in healthy adult volunteers (Study 1 and Study 2). In both studies, adverse events (AEs), clinical laboratory tests, vital signs (supine blood pressure and pulse rate), and electrocardiograms (ECGs) were evaluated. Overall, in Study 1, Compound 1 was well-tolerated.

[0160] Compound 1, when administered as multiple doses up to 200 mg, was generally well tolerated in the healthy subject population studied. In Study 1, the effects upon biomarkers of relevance for the treatment of alcohol dependence were investigated. Five clusters of an Addiction Research Center Inventory Questionnaire (ARCI-49) were used to compare the effect of Compound 1 vs. placebo: Morphine-Benzphetamine Group Scale measuring euphoria; Lysergic-Acid-Diethylamide Group Scale estimating dysphoric and somatic changes; Pentobarbital-

Chlorpromazine-Alcohol Group Scale measuring sedation; Benzedrine Group (BG) Scale measuring intellectual efficiency and energy; Amphetamine Group Scale measuring effects of d-amphetamine, respectively. No systematic pattern or dose-response for the change from baseline or for the difference over placebo in each cluster was observed.

[0161] In summary, single, oral doses up to 800 mg and multiple doses up to 200 mg of Compound 1 were well-tolerated by healthy male and female subjects.

Example 4: Phase 2 Clinical Studies

[0162] Cohort A of the Phase 2 Study includes a 6-week, multiple-dose, dose escalation study of Compound 1 for the treatment of adults with classic CAH. After screening, eligible patients will be enrolled into a 6-week treatment period followed by a 4-week washout/safety follow-up period.

[0163] This cohort will be conducted in approximately 9 patients, who will receive Compound 1 daily for up to 6 weeks. Compound 1 will be administered as an oral daily dose. Patients will undergo titration of Compound 1 through three escalating dosage strengths at 2-week intervals. Patients will have overnight PK/PD assessments performed at baseline, which include a pre-dose overnight assessment and a post-dose overnight assessment for PK/PD following administration of the first dose. At the end of each 2-week dosing period, patients will return for single overnight visits for steady-state PK/PD assessments. A follow-up outpatient visit will occur 30 days after their last dose. Upon completion of the initial cohort (Cohort A), the study will proceed to a multiple ascending dose (MAD) design with up to 3 sequential cohorts (Cohorts B, C, and D) to further evaluate the safety, PK, and PD of various SPR001 dosing regimens and to identify an optimal dose regimen. Each cohort will undergo a 2-week run-in period, a 2-week treatment period, and a 30-day washout and safety follow-up period. During the run-in period, which will occur during screening, subjects will document in a paper diary each dose of glucocorticoid medication taken, the time of each meal, and the time they went to bed and woke up each day, to ensure compliance with background glucocorticoid regimens and the stability of their daily routine.

[0164] Patients in Cohort B will receive study drug at 200 mg BID, with a dose in the morning and a dose in the evening, either with a meal or consumption of a standardized snack. For Cohorts C and D, the dose level and the frequency and timing of dosing will be determined based on interim data from the previous cohorts. However, the dose level of each successive cohort will be capped at twice the daily dose level of the previous cohort.

Study Design

- Study Type: Interventional
- Primary Purpose: Treatment

- Study Phase: Phase 2
- Interventional Study Model: Sequential Assignment
- Number of Cohorts: Up to 4
- Masking: No masking
- Allocation: Non-Randomized
- Enrollment: Up to approximately 27 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Cohort A The first cohort of 9 patients will be administered Compound 1 at dose strength of 200 mg daily for 2 weeks, and escalating through 600 mg per day for 2 weeks and 1,000 mg per day for 2 weeks.	Drug: Compound 1 200-mg capsules
Experimental: Cohort B Cohort B patients will be administered Compound 1 at a dose strength of 200 mg twice daily (BID) for 2 weeks.	Drug: Compound 1 200-mg capsules
Experimental: Cohort C The dose/dose regimen for Cohort C will be determined based on an interim review of safety and PK/PD data from the previous Cohorts	Drug: Compound 1 50-mg or 200 mg capsules
Experimental: Cohort D The dose/dose regimen for Cohort C will be determined based on an interim review of safety and PK/PD data from the previous Cohorts	Drug: Compound 1 50-mg or 200 mg capsules

Outcome Measures

Primary Outcome Measure:

1. To evaluate the safety of Compound 1 in subjects with CAH.
2. To assess the efficacy of Compound 1 in subjects with classic CAH as measured by percent and absolute change in 17-OHP compared to baseline.

Secondary Outcome Measure:

3. To explore the dose(s) of Compound 1 that cause pharmacodynamics changes in plasma concentrations of ACTH, androstenedione, and testosterone, as measured by the absolute and percent change from baseline by dose.
4. To determine pharmacokinetics of Compound 1 in subjects with CAH.
5. To explore potential relationships between pharmacodynamics and pharmacokinetics.

Exploratory

6. To explore the dose(s) of Compound 1 that cause changes in pharmacodynamics biomarkers in urine, as measured by the absolute and percent change from baseline by dose.

Eligibility

- Minimum Age: 18 Years
- Maximum Age:
- 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 17-OHP at screening
- 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.

Results:

The phase 2 study showed that Compound 1 was generally well-tolerated. The study established a range of safe doses after exploring a wide range of doses (5-fold range) (see FIG. 1).

[0165] With respect to patient-level response to Compound 1, 80% showed reduced ACTH (see FIG. 2). Generally, attenuation of ACTH demonstrates target engagement and functional CRF₁ receptor antagonism. 80% of patient subjects demonstrated reduction in ACTH. 70% of subject demonstrated more than 25% reduction in ACTH. 40% of subjects were in the normal range after treatment.

[0166] A reduction of 17-OHP demonstrates “control” of the disease based on Standard guidelines. This allows for steroid taper. 80% of subjects demonstrated reduction in 17-OHP (see FIG. 3). 50% of subjects demonstrated more than 25% reduction in 17-OHP. 50% of subjects were within the guideline range (1200 ng/dL) after treatment.

[0167] Compound 1 attenuates morning rise in A4 which indicates an ability to control excess androgen production and associated symptoms (see FIG. 4). 100% of subjects demonstrated reduction in Androstenedione (at various doses). 60% of subjects demonstrated more than 25%

reduction in Androstenedione. 50% of subjects were within normal reference range after treatment.

Example 5: 3-Month Phase 2 Study

[0168] This is a 3-month Phase 2 study to evaluate the safety and efficacy of Compound 1 in subjects with classic CAH. This study will investigate the extended use of Compound 1 over a 3-month period in combination with replacement glucocorticoids and mineralocorticoids in the treatment of CAH.

[0169] This study will enroll up to approximately 24 eligible subjects who will receive Compound 1 daily for up to 3-months. Compound 1 will be administered as an oral daily dose. At the end of each 2-week dosing period, patients will return for morning laboratory assessments. A follow-up outpatient visit will occur 30 days after their last dose.

Study Design

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 2
- Interventional Study Model: Sequential Assignment
- Number of Arms: 1
- Masking: No Masking
- Allocation: Non-Randomized
- Enrollment: Up to approximately 24 [anticipated]

Outcome Measures*Primary Outcome Measure:*

1. To evaluate the safety of Compound 1 in subjects with CAH.

Second Outcome Measure:

2. To evaluate the efficacy of Compound 1 in subjects with CAH in terms of changes in hormones.

Exploratory:

3. To evaluate the effect of Compound 1 on quality of life, metabolic parameters, exploratory adrenal hormones, and semen analysis in subjects with CAH.

Eligibility:

- Minimum Age: 18 Years
- Maximum Age:
- 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 17-OHP at screening
- 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.

Example 6: Adolescent Study

[0170] This is a Phase 2, open-label, multiple-dose study designed to provide proof of concept for the use of Compound 1 to treat adolescents 12 to 17 years of age with classic CAH. The study will evaluate the safety, efficacy, and PK of 2 weeks of treatment with Compound 1. Each subject will undergo a 2-week diary run-in period during screening, a 2-week treatment period, and a 30-day washout and safety follow-up period.

[0171] An adaptive design with up to 3 sequential dose cohorts (Cohorts 1, 2, and 3) is planned to identify an optimal dose strength and regimen in adolescents with classic CAH. Each cohort will initially enroll 3 subjects and may later enroll 3 more subjects based on interim data from the first 3 subjects, for a total of 6 subjects per cohort. However, if safety, efficacy, and PK results from 6 subjects are inconclusive, a cohort may be expanded up to a maximum of 12 subjects. Cohort 1 will receive study drug at 200 mg QD. Cohorts 2 and 3 will be sequentially activated only if further investigation of an optimal dose strength or regimen is required; the dose strength and frequency and timing of dosing for these cohorts will be determined based on interim data from the previous cohort(s). However, the dose strength administered to each successive cohort will be capped at twice the daily dose strength administered to the previous cohort.

[0172] This study will enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). In practice, CAH patients are typically treated

with supraphysiologic doses of GCs which are both toxic and not effective in many adolescent patients. In this population, GCs are associated with multiple well-described short- and long-term toxicities including: growth retardation, weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

[0173] The objective of treatment of this patient population with Compound 1 is reduction (or normalization) of key hormonal outcome measures which could allow reduction of their GC replacement requirements which will improve clinical outcomes of concern, including growth velocity. Improvement of hormonal outcome measures in this population are also expected to delay premature puberty and bone maturation, ultimately leading to improvements in height in adolescents with CAH.

Outcome Measures

Primary Outcome Measures:

1. To evaluate the safety of Compound 1 in adolescent subjects with CAH.

Secondary Outcome Measures:

2. To evaluate the dose(s) of Compound 1 that cause changes in key pharmacodynamics biomarkers in blood in adolescent subjects with CAH.
3. To investigate the effect of Compound 1 on quality of life in adolescent subjects with CAH.
4. To determine the pharmacokinetics of Compound 1 in adolescent subjects with CAH.
5. To investigate potential relationships between pharmacodynamics and pharmacokinetics in adolescent subjects with CAH.

Exploratory

6. To explore the dose(s) of Compound 1 that cause changes in exploratory pharmacodynamics biomarkers in blood and urine in adolescent subjects with CAH.

Eligibility Criteria

Inclusion Criteria:

- Male and female subjects 12 to 17 years of age, inclusive
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP at screening
- On a stable regimen of glucocorticoid replacement for 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.

Example 7: Phase 3 Clinical Studies

[0174] This is a 24-week, randomized, double-blind, placebo-controlled study of Compound 1 for the treatment of classic CAH. After screening, eligible patients will be enrolled into a 24-week treatment period followed by a 4-week safety follow-up period.

[0175] Subjects in the study will be randomized in a 1:1 ratio to either receive Compound 1 or a matching placebo for up to 24 weeks. Compound 1 or a placebo will be administered as an oral daily dose. Patients will return approximately monthly for study visits. A follow-up outpatient visit will occur 30 days after their last dose. It is initially planned that up to approximately 150 patients will be enrolled.

[0176] Consistent with the design of the Phase 2 study, the Phase 3 clinical study will seek to enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen: hydrocortisone, prednisone/prednisolone, and/or dexamethasone). In practice, CAH patients are typically treated with supraphysiologic doses of GCs which are both toxic and not effective in the majority of patients. GCs are associated with multiple well-described short- and long-term toxicities in adults including: excessive weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

Study Design:

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 3
- Interventional Study Model: Randomized Controlled Trial
- Allocation: Randomized
- Enrollment: 150 [Anticipated]

Outcome Measures*Primary Outcome Measures*

1. Evaluate efficacy of Compound 1 in reducing A4 and 17-OHP in patients with CAH.

Secondary Outcome Measures

2. Evaluate efficacy of Compound 1 in patients with CAH in terms of changes in key hormones.
3. Evaluate efficacy of Compound 1 in improving quality of life and/or mood in patients with CAH.

4. Evaluate efficacy of Compound 1 in improving hyperandrogenic symptoms in patients with CAH.
5. Evaluate efficacy of Compound 1 in improving metabolic parameters in patients with CAH.
6. Evaluate safety of Compound 1 in patients with CAH.

Eligibility

- Minimum age: 16 Years
- Maximum Age:
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria*Inclusion Criteria:*

- Male and female patients age 16 or older.
- Document diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated 17-OHP
- 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.

Example 8: Phase 3 OLE and steroid sparing studies

[0177] Upon completion of the study described in Example 7, eligible patients will then be offered the opportunity to enroll into an open label extension study lasting up to 1 year. The open label study will allow all eligible patients to receive active study drug during their participation in the Phase 3 program. Patients will undergo study assessments every 1-3 months during the open label phase, and will be evaluated for long-term safety and efficacy (including both hormonal endpoints and long-term clinical outcome measures of concern in this population).

[0178]

[0179] A further study may seek to enroll patients with inadequately controlled CAH despite an existing glucocorticoid (GC) regimen (including any currently-available regimen:

hydrocortisone, prednisone/prednisolone, and/or dexamethasone). Such CAH patients are typically treated with supraphysiologic doses of GCs which are both toxic and not effective in the majority of patients. GCs are associated with multiple well-described short- and long-term toxicities in adults including: excessive weight gain, hypertension, hyperglycemia, hyperlipidemia, and Cushingoid features.

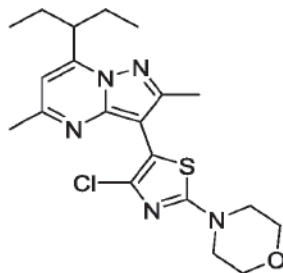
[0180] [0159] Following a period of treatment (for example 12 weeks) during the dose of GC will be kept stable, patients in this study will have their dose of GC progressively reduced from a supraphysiologic dose to a lower dose at or close to a dose equivalent to a physiologic dose of GC.

[0181] 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. 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 of the invention 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.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof,

- wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.
2. The method of claim 1, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1200 mg/day.
 3. The method of claim 1 or 2, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1000 mg/day.
 4. The method of any one of claims 1 to 3, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day.
 5. The method of any one of claims 1 to 4, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 100 mg/day and about 600 mg/day.
 6. The method of any one of claims 1 to 5, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day.
 7. The method of any one of claims 1 to 6, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.
 8. The method of any one of claims 1 to 7, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles.
 9. The method of claim 8, wherein the average size of the microparticles is between about 1 μm and about 20 μm .

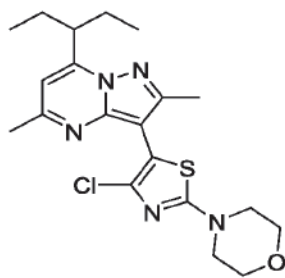
10. The method of claim 8 or 9, wherein the average size of the microparticles is between about 5 μm and about 15 μm .
11. The method of any one of claims 8 to 10, wherein the average size of the microparticles is less than about 10 μm .
12. The method of any one of claims 1 to 11, wherein the pharmaceutical composition is in the form of a capsule or a tablet.
13. The method of any one of claims 1 to 12, wherein the pharmaceutical composition is in the form of a capsule.
14. The method of claim 13, wherein the capsule is a hard gelatin capsule.
15. The method of claim 13, wherein the capsule is a soft gelatin capsule.
16. The method of any one of claims 13 to 15, 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.
17. The method of any one of claims 13 to 16, wherein the pharmaceutical composition is free of additional excipients.
18. The method of any one of claims 13 to 16, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.
19. The method of any one of claims 1 to 12, wherein the pharmaceutical composition is in the form of a tablet.
20. The method of claim 19, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.
21. The method of any one of claims 1 to 20, wherein the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
22. The method of any one of claims 1 to 21, wherein the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
23. The method of any one of claims 1 to 22, wherein the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
24. The method of any one of claims 1 to 23, wherein the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

25. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
26. The method of any one of claims 1 to 23, wherein the pharmaceutical composition comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
27. The method of any one of claims 1 to 23, wherein the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
28. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
29. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
30. The method of any one of claims 1 to 23, wherein the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
31. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
32. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
33. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
34. The method of any one of claims 1 to 24, wherein the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
35. The method of any one of claims 1 to 25, wherein the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

36. The method of any one of claims 1 to 25, wherein the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
37. The method of any one of claims 1 to 25, wherein the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
38. The method of any one of claims 1 to 25, wherein the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
39. The method of any one of claims 1 to 25, wherein the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
40. The method of any one of claims 1 to 39, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 2 to about 6 hours in a subject.
41. The method of any one of claims 1 to 40, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 3 to about 5 hours in a subject.
42. The method of any one of claims 1 to 40, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 6 hours in a subject.
43. The method of any one of claims 1 to 41, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 5 hours in a subject.
44. The method of any one of claims 1 to 41, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 4 hours in a subject.
45. The method of any one of claims 1 to 41, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 3 hours in a subject.
46. The method of any one of claims 1 to 45, wherein the pharmaceutical composition is administered in the fed state.
47. The method of any one of claims 1 to 45, wherein the pharmaceutical composition is administered in the fasted state.
48. The method of any one of claims 1 to 47, wherein the pharmaceutical composition is administered once a day.
49. The method of any one of claims 1 to 47, wherein the pharmaceutical composition is administered twice a day.
50. The method of any one of claims 1 to 47, wherein the pharmaceutical composition is administered three times a day.
51. The method of any of claims 1 to 50, further comprising administering a glucocorticoid.

52. The method of claim 51, wherein the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
53. The method of claim 52, wherein the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount.
54. The method of claim 52, wherein the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.
55. The method of any one of claims 52 to 54, wherein the symptoms associated with high-dose glucocorticoid therapy are reduced.
56. The method of claim 55, wherein the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis.
57. The method of any one of claims 51 to 56, wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.
58. The method of any one of claims 51 to 57, wherein the glucocorticoid is hydrocortisone.
59. The method of claim 58, wherein the hydrocortisone is administered at a dose less than about 15 mg/day.
60. The method of claim 58 or 59, wherein the hydrocortisone is administered at a dose less than about 10 mg/day.
61. The method of any one of claims 58 to 60, wherein the hydrocortisone is administered at a dose less than about 5 mg/day.
62. The method of any one of claims 51 to 61, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently.
63. The method of any one of claims 51 to 62, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially.
64. The method of any one of claims 51 to 62, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours.
65. The method of any one of claims 51 to 62, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 8 hours.

66. The method of any one of claims 51 to 62, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 2 hours.
67. The method of any one of claims 51 to 62, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 30 minutes.
68. The method of any one of claims 1 to 67, further comprising administering a mineralocorticoid.
69. The method of claim 68, wherein the mineralocorticoid is fludrocortisone.
70. The method of any one of claims 1 to 69, wherein the pharmaceutical composition is administered at bedtime.
71. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered less than about 4 hours before sleep.
72. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered less than about 2 hours before sleep.
73. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered less than about 30 mins before sleep.
74. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered in the evening.
75. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered at about 10 pm at night.
76. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered at or before the expected circadian release of adrenocorticotrophic hormone (ACTH).
77. The method of any one of claims 1 to 70, wherein the pharmaceutical composition is administered about 3-4 hours before the expected circadian release of adrenocorticotrophic hormone (ACTH).
78. The method of any one of claims 1 to 77, wherein CAH is classic CAH.
79. The method of any one of claims 1 to 77, wherein CAH is non-classic CAH.
80. A method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising:
 - (iv) measuring a hormone level in the subject in need thereof;
 - (v) administering Compound 1:



or a pharmaceutically acceptable salt or solvate thereof;

(vi) repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of compound 1.

81. The method of claim 80, wherein the hormone is 17 α -Hydroxyprogesterone (17-OHP), adrenocorticotrophic hormone (ACTH), testosterone, or androstenedione.
82. The method of claim 81, wherein the hormone is 17-OHP, and the pre-determined range is from about 200 ng/dL to about 400 ng/dL.
83. The method of claim 81, wherein the hormone is ACTH, and the pre-determined range is below about 100 pg/mL.
84. The method of claim 81, wherein the hormone is testosterone and the pre-determined range is from about 14 ng/dL to about 76 ng/dL.
85. The method of claim 81, wherein the hormone is androstenedione and the pre-determined range is from about 30 ng/dL to about 150 ng/dL in males.
86. The method of claim 81, wherein the hormone is androstenedione and the pre-determined range is from about 40 ng/dL to about 200 ng/dL in females.
87. The method of any one of claims 80 to 86, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1600 mg/day.
88. The method of any one of claims 80 to 87, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1200 mg/day.
89. The method of any one of claims 80 to 88, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 1000 mg/day.
90. The method of any one of claims 80 to 89, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 800 mg/day.
91. The method of any one of claims 80 to 90, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and about 600 mg/day.

92. The method of any one of claims 80 to 91, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 200 mg/day and 400 mg /day.
93. The method of any one of claims 80 to 92, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 200 mg /day.
94. The method of any one of claims 80 to 86, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1600 mg/day.
95. The method of claim 94, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1200 mg/day.
96. The method of claims 94 or 95, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 1000 mg/day.
97. The method of any one of claims 94 to 96, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 800 mg/day.
98. The method of any one of claims 94 to 97, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and about 600 mg/day.
99. The method of any one of claims 94 to 98, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between about 50 mg/day and 400 mg /day.
100. The method of any one of claims 94 to 99, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose between 50 mg/day and 200 mg/day.
101. The method of any one of claims 94 to 99, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at a dose of about 50 mg /day.
102. The method of any one of claims 80 to 101, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is in the form of microparticles.
103. The method of claim 102, wherein the average size of the microparticles is between about 1 μm and about 20 μm .
104. The method of claim 102 or 103, wherein the average size of the microparticles is between about 5 μm and about 15 μm .

105. The method of any one of claims 102 to 104, wherein the average size of the microparticles is less than about 10 μm .
106. The method of any one of claims 80 to 105, wherein Compound 1 is formulated in a pharmaceutical composition in the form of a capsule or a tablet.
107. The method of claim 106, wherein the pharmaceutical composition is in the form of a capsule.
108. The method of claim 107, wherein the capsule is a hard gelatin capsule.
109. The method of claim 107, wherein the capsule is a soft gelatin capsule.
110. The method of any one of claims 106 to 109, 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.
111. The method of any one of claims 106 to 110, wherein the pharmaceutical composition is free of additional excipients.
112. The method of any one of claims 106 to 110, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.
113. The method of claim 106, wherein the pharmaceutical composition is in the form of a tablet.
114. The method of claim 113, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.
115. The method of any one of claims 106 to 114, wherein the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
116. The method of any one of claims 106 to 115, wherein the pharmaceutical composition comprises between about 5 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
117. The method of any one of claims 106 to 116, wherein the pharmaceutical composition comprises between about 10 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
118. The method of any one of claims 106 to 117, wherein the pharmaceutical composition comprises between about 10 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
119. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises between about 10 mg and about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

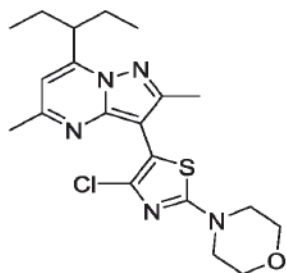
120. The method of any one of claims 106 to 117, wherein the pharmaceutical composition comprises between about 50 mg and about 500 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
121. The method of any one of claims 106 to 117, wherein the pharmaceutical composition comprises between about 100 mg and about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
122. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises between about 100 mg and about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
123. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises between about 150 mg and about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
124. The method of any one of claims 106 to 117, wherein the pharmaceutical composition comprises about 400 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
125. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 300 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
126. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 250 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
127. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 200 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
128. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 150 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
129. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 100 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
130. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 80 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.

131. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 60 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
132. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 50 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
133. The method of any one of claims 106 to 118, wherein the pharmaceutical composition comprises about 30 mg of Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
134. The method of any one of claims 106 to 133, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 2 to about 6 hours in a subject.
135. The method of any one of claims 106 to 118, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 3 to about 5 hours in a subject.
136. The method of any one of claims 106 to 118, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 6 hours in a subject.
137. The method of any one of claims 106 to 135, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 5 hours in a subject.
138. The method of any one of claims 106 to 135, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 4 hours in a subject.
139. The method of any one of claims 106 to 135, wherein the pharmaceutical composition provides a Compound 1 $T_{\max}$ of about 3 hours in a subject.
140. The method of any one of claims 106 to 139, wherein the pharmaceutical composition is administered in the fed state.
141. The method of any one of claims 106 to 140, wherein the pharmaceutical composition is administered in the fasted state.
142. The method of any one of claims 106 to 141, wherein the pharmaceutical composition is administered once a day.
143. The method of any one of claims 106 to 141, wherein the pharmaceutical composition is administered twice a day.
144. The method of any one of claims 106 to 141, wherein the pharmaceutical composition is administered three times a day.
145. The method of any of claims 80 to 144, further comprising administering a glucocorticoid.

146. The method of claim 145, wherein the amount of glucocorticoid administered is reduced as compared to a method not comprising administering Compound 1, or a pharmaceutically acceptable salt or solvate thereof.
147. The method of claim 145, wherein the amount of glucocorticoid used is reduced from a supraphysiologic amount to a physiologic amount.
148. The method of claim 145, wherein the amount of glucocorticoid is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%.
149. The method of any one of claims 145 to 148, wherein the symptoms associated with high-dose glucocorticoid therapy are reduced.
150. The method of claim 149, wherein the symptoms associated with high-dose glucocorticoid therapy are obesity, insulin resistance, metabolic abnormalities, hypertension, cardiovascular diseases, or osteoporosis.
151. The method of any one of claims 145 to 150, wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.
152. The method of any one of claims 145 to 151, wherein the glucocorticoid is hydrocortisone.
153. The method of claim 152, wherein the hydrocortisone is administered at a dose less than about 15 mg/day.
154. The method of claim 152 or 153, wherein the hydrocortisone is administered at a dose less than about 10 mg/day.
155. The method of any one of claims 152 to 154, wherein the hydrocortisone is administered at a dose less than about 5 mg/day.
156. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered concurrently.
157. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially.
158. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 24 hours.

159. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 8 hours.
160. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 2 hours.
161. The method of any one of claims 152 to 155, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, and the glucocorticoid are administered sequentially within 30 minutes.
162. The method of any one of claims 80 to 161, further comprising administering a mineralocorticoid.
163. The method of claim 162, wherein the mineralocorticoid is fludrocortisone.
164. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at bedtime.
165. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 4 hours before sleeping.
166. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 2 hours before sleeping.
167. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered less than about 30 mins before sleeping.
168. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered in the evening.
169. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at 10 pm at night.
170. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered at or before the expected circadian release of adrenocorticotrophic hormone (ACTH).
171. The method of any one of claims 80 to 163, wherein Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is administered about 3-4 hours before the expected circadian release of adrenocorticotrophic hormone (ACTH).
172. The method of any one of claims 80 to 171, wherein CAH is classic CAH.
173. The method of any one of claims 80 to 171, wherein CAH is non-classic CAH.
174. A method of any one of claims 1 to 173, wherein the subject in need thereof is from about 12 years of age to about 20 years of age.

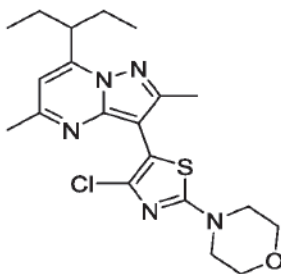
175. A method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof,

wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

176. A method of claim 175, wherein the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism and alopecia.
177. A method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering a pharmaceutical composition

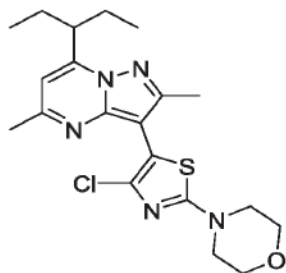


comprising Compound 1:

; or a pharmaceutically acceptable salt

or solvate thereof, wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

178. A method of improving metabolic symptoms in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:

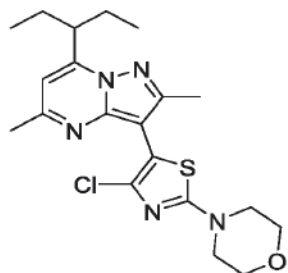


; or a pharmaceutically acceptable salt or solvate thereof,

wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day.

179. A method of claim 178, wherein the metabolic symptoms are selected from the group consisting of body weight, BMI, waist circumference, blood pressure and glycemic control.

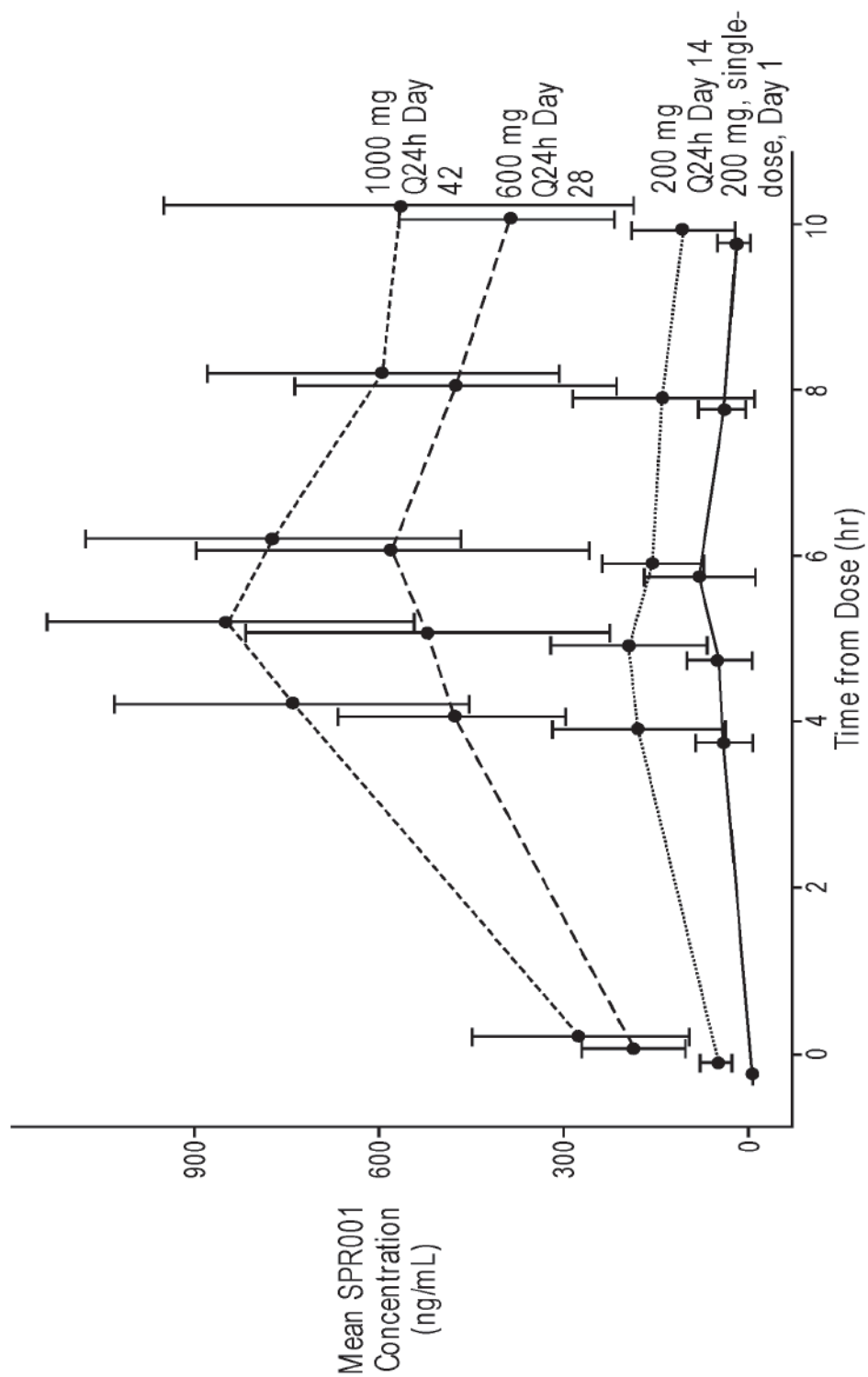
180. A method of improving quality of life in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 1:



; or a pharmaceutically acceptable salt or solvate thereof,

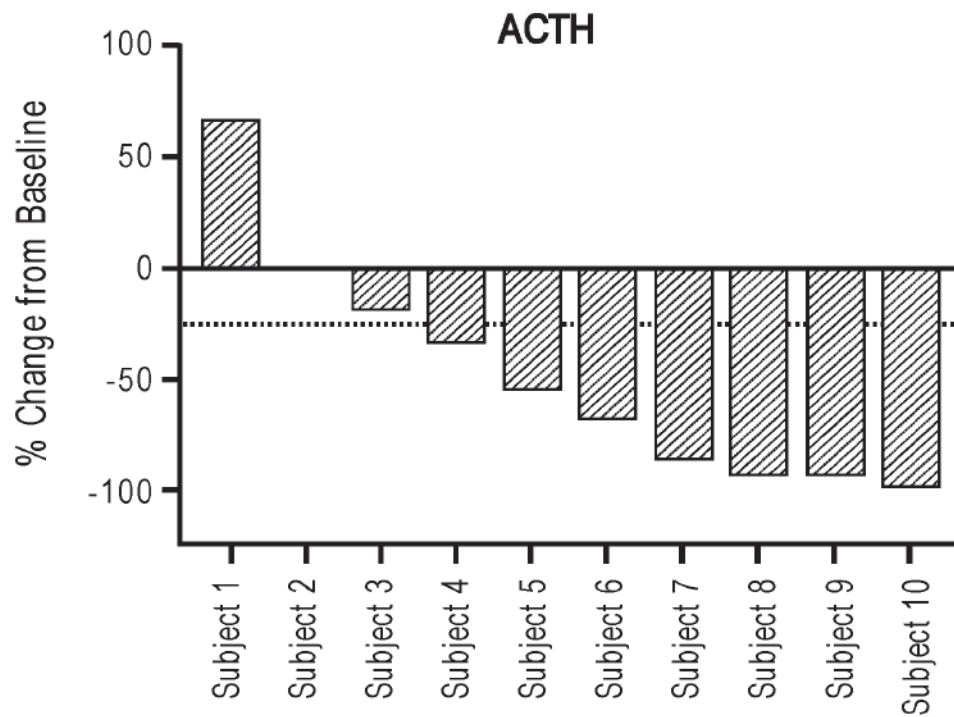
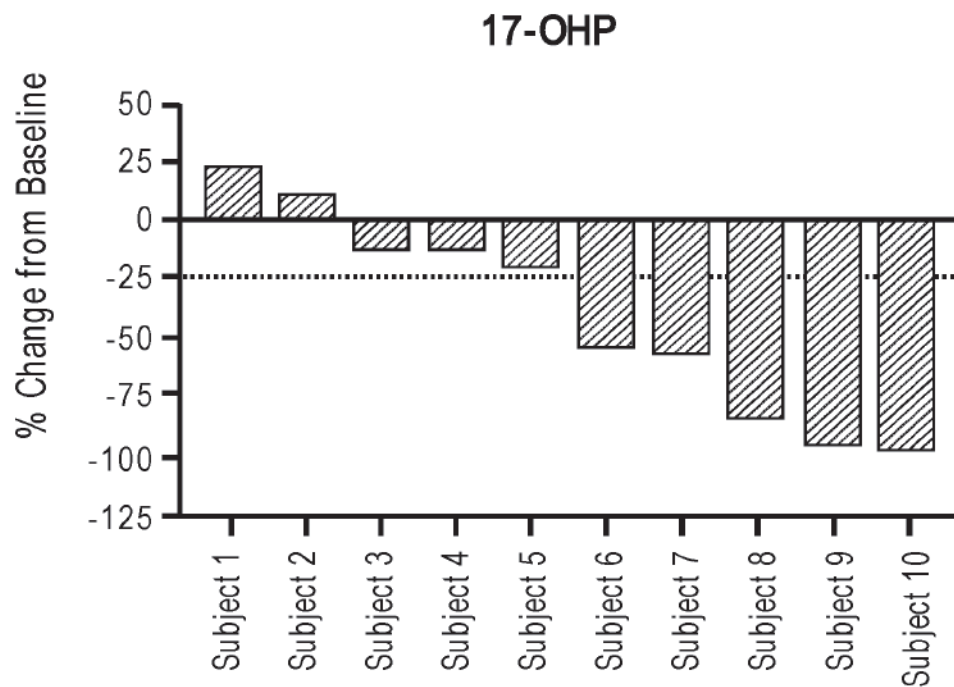
wherein Compound 1 is administered at a dose between about 50 mg/day and about 1600 mg/day, wherein treatment results in an improved quality of life.

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**FIG. 1**

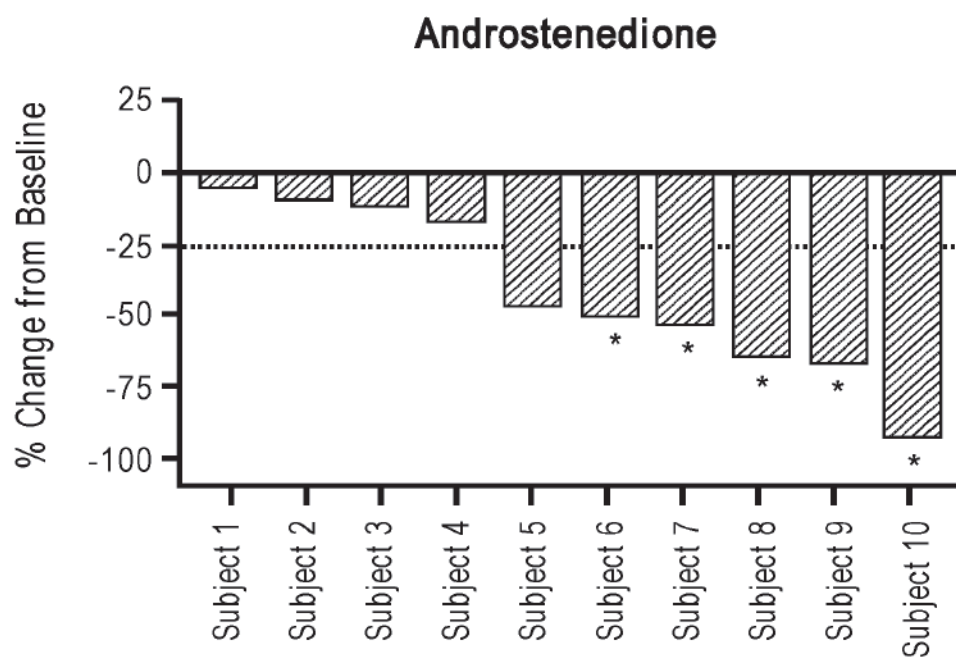
SUBSTITUTE SHEET (RULE 26)

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**FIG. 2****FIG. 3**

SUBSTITUTE SHEET (RULE 26)

3/3

**FIG. 4**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/46760

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/415; 31/425; 31/519; C07D 487/04; A61P 5/24 (2018.01)
CPC - A61K 31/41; A61K 31/519; C07D 487/04; C07D 401/04

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.
Y	US 8,030,304 B2 (CHEN et al.) 04 October 2011 (04.10.2011) Col 1, ln 10-15; Col 2, ln 51-56; Col 3, ln 8-12; Col 5, ln 63 to Col 6, ln 4; Col 6, ln 11-13; Col 32, Example 16	1-3, 80-87, 94-95; 175-180
Y	TURCU et al. 'Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency', J. Clin. Endocrinol. Metab. 2016, Vol. 101(3), pp. 1174-1180. Abstract; pg. 1177, Table 2; pg. 1179, Table 3; pg. 1179, Col 2, para 2 to pg. 1180, Col 1, para 2	1-3, 80-87, 94-95; 175-180
A	US 2017/0020877 A1 (NEUROCRINE BIOSCIENCES, INC.) 26 January 2017 (26.01.2017) ENTIRE DOCUMENT	1-3, 80-87, 94-95; 175-180
A	US 2010/0155595 A1 (GHOSHAL et al.) 24 June 2010 (24.06.2010) ENTIRE DOCUMENT	1-3, 80-87, 94-95; 175-180
A	Lee et al. 'Attenuated Forms of Congenital Adrenal Hyperplasia due to 21-hydroxylase Deficiency', Journal of Clin Endocrin Metab 1982, Vol. 55, pp. 866-871. ENTIRE DOCUMENT	1-3, 80-87, 94-95; 175-180

☐ 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

"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

25 SEPTEMBER 2018

Date of mailing of the international search report

24 OCT 2018

Name and mailing address of the ISA/US

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Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/46760

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.: 4-79, 88-93 and 96-174
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.

Patents

JP2002513382A



Azolotriazines and azolopyrimidines

Abstract

translated from Japanese

(57) Abstract: Corticotropin-releasing factor (CRF) antagonists of formula (I) or (II) and the treatment and immunology of anxiety, depression, and other psychiatric and neurological disorders. Use thereof in the treatment of colon irritability associated with a medical, cardiovascular or heart disease and psychopathological disorders and stress.

JP2002513382A

Japan

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Other languages: Japanese

Inventor: アルバニティス, アルギリオス, ゲオルジウス, コーバット, コバート, ジョン,

Worldwide applications

1997 SI 6N EE 6K FL 02 9R GA 6A NZ 98 IL NR 1998 IL 1999 NO 2601 GN 2002 CN 2004 JP 2005 AR

Application JP50723398A events

1997-07-23 Application filed by デュポン ファーマシューテイカ ルス カンパニー

2002-05-08 Publication of JP2002513382A

2005-12-02 Publication of JP2002513382A5

2011-06-15 Application granted

2011-06-15 Publication of JP4794821B2

2017-07-23 Anticipated expiration

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Claims (1)

Hide Dependent

translated from Japanese

[Claims] 1. Affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, Supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa or other Eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular disease illness or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, bleeding Stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcer, muscle atrophy Treatment of atrophic lateral sclerosis, hypoglycemia, or a disorder by antagonizing CRF including but not limited to CRF-induced or promoted disorders that are achieved or facilitated A method of treating a mammal, such as a disorder not limited to) Compound, And its isomers, its stereoisomers, or mixtures of its stereoisomers, and drugs A mammal is administered a therapeutically effective amount of a pharmaceutically acceptable salt or prodrug thereof, including giving in the above formula, A is N or CR; Z is H or CR^{Two} And Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, fura Nil, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzof Ranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyran 3,4-dihydro-1,2-benzopyranlyl, tetralinyl (each of Ar is 1-5 R^{Four} And each Ar is substituted with an unsaturated carbon atom, joined) R is independently H, C in each case, C_{Four} Alkyl, C_{Two} C_{Four} Alkenyl, C_{Two} C_{Four} Alkynyl, C_{Three} C₆ Cycloalkyl, C_{Four} C₇ Cycloalkyl, C_{Four} C₇ Cycloalkyl, halo, CN, C₁ C_{Four} Selected from haloalkyl, R¹ Are independently H, C in each case, C_{Four} Alkyl, C_{Two} C_{Four} Alkene, C_{Two} C_{Four} Alkynyl, halo, CN, C₁ C_{Four} Haloalkyl, C₁ C₁₂ Hld Roxyalkyl, C_{Two} C₁₂ Alkoxyalkyl, C_{Two} C_{Ten} Cyanoalkyl, C_{Three} C₆ Cycloalkyl, C_{Four} C_{Ten} Cycloalkylalkyl, NR⁶ R^{Ten}, C₁ C_{Four} Alkyl-NR⁶ R^{Ten}, NR⁶ COR^{Ten}, OR¹¹, SH or S (O)_n R¹² Selected from R^{Two} is H, C₁ C_{Four} Alkyl, C_{Two} C_{Four} Alkenyl, C_{Two} C_{Four} Alkynyl, C_{Three} C₆ Cycloalkyl, C_{Four} C_{Ten} Cycloalkylalkyl, C₁ C_{Four} Hydro Xyalkyl, halo, CN, NR⁶ R⁷, NR⁶ COR^{Ten}, NR⁶ S (O)_n R⁷, S (O)_n NR⁶ R⁷, C₁ C_{Four} Haloalkyl, -OR⁷, SH or -S (O)_n R¹² Selected from R^{Three} is -H, OR⁷, SH, S (O)_n R¹³, COR⁷, CO_{Two} R⁷, OC (O) R¹³, NR⁶ COR⁷, N (COR⁷)_{Two}, NR⁶ CONR⁶ R⁷, NR⁶ CO_{Two} R¹³, NR⁶ R⁷, NR⁶ R^{7a}, N (OR⁷) R⁶, CONR⁶ R⁷, Aryl, heteroaryl And heterocyclic groups, Or -C₁ C_{Ten} Alkyl, C_{Two} C_{Ten} Alkenyl, C_{Two} C_{Ten} Alkynyl, C_{Three} C₆ Cycloalkyl, C_{Four} C₆ Cycloalkenyl, C_{Four} C₁₂ Cycloalkylalkyl Or C₆ C_{Ten} Cycloalkenylalkyl (each group is independently C₁ C₆ Alkyl, C_{Three} C₆ Cycloalkyl, halo, C₁ C_{Four} Halo Alkyl, cyano, OR^{Fifteen}, SH, S (O)_n R¹³, COR^{Fifteen}, CO_{Two} R^{Fifteen}, OC (O) R¹³, NR⁶ COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶ CONR⁶ R^{Fifteen}, NR⁶ CO_{Two} R¹³, NR⁶ R^{Fifteen}, CONR⁶ R^{Fifteen}, Aryl, heteroaryl and hetero Optionally substituted with 1 to 5 substituents selected from cyclic groups), R^{Four} is independently in each case C₁ C_{Ten} Alkyl, C_{Two} C_{Ten} Alkenyl, C_{Two} C_{Ten} Alkynyl, C_{Three} C₆ Cycloalkyl, C_{Four} C₁₂ Cycloalkyl, halo, NO_{Two}, halo, CN, C₁ C_{Four} Haloalkyl, NR⁶ R⁷, NR⁶ COR⁷, NR⁶ CO_{Two} R⁷, COR⁷, OR⁷, CONR⁶ R⁷, CO (NOR⁹) R⁷, CO_{Two} R⁷, Or S (O)_n R⁷ (C₁ C_{Ten} Alkyl, C_{Two} C_{Ten} Alkenyl, C_{Two} C_{Ten} Alkynyl, C_{Three} C₆ Cycloalkyl and C_{Four} C₁₂ Cycloalkylalkyl Each independently represents in each case C₁ C_{Four} Alkyl, NO_{Two}, halo, CN, NR⁶ R⁷, NR⁶ COR⁷, NR⁶ CO_{Two} R⁷, COR⁷, OR⁷, CONR⁶ R⁷, CO_{Two} R⁷, CO (NOR⁹) R⁷, Or S (O)_n R⁷ 1-3 selected from Optionally substituted with) substituents, R⁶ And R⁷, R^{6a} And R^{7a} Are, independently, in each case, -H, -C₁ C_{Ten} Alkyl, C_{Three} C_{Ten} Alkenyl, C_{Three} C_{Ten} Alkynyl, halogen C with 1 to 10 atoms, -C₁ C_{Ten} Haloalkyl, C_{Two} C₆ Alkoxyalkyl, C_{Three} C₆ Cycloalkyl, C_{Four} C₁₂ Cycloalkylalkyl, C_{Four} C_{Ten} Cyclo Alkenyl, or C₆

C₁₋₆Cycloalkenylalkyl (each group is in each case independently C₁₋₆Alkyl, C₁₋₆Cycloalkyl, halo, C₁₋₆F₄Alkoalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from , Aryl, aryl (C₁₋₆F₄Alkyl), heteroaryl, heteroaryl Le (C₁₋₆F₄Alkyl), a heterocyclic group or a heterocyclic (C₁₋₆F₄Alkyl) Selected or Alternatively, NR⁶R⁷ And NR⁶R⁷ Are independently piperidine, pyrrolidine, Perazine, N-methylpiperazine, morpholine or thiomorpholine (each is from 1 to 3 C₁₋₆F₄ Optionally substituted with an alkyl group), R⁸ is independently H or C in each case C₁₋₆F₄ Selected from alkyl, R⁶ And R⁷ Are independently H, C in each case C₁₋₆F₄ Alkyl, or C_{Three-6} Selected from cycloalkyl, R¹¹ is H, C₁₋₆F₄Alkyl, C₁₋₆F₄Alkoalkyl or C_{Three-6} Cycloa Selected from Luqil, R¹² is C₁₋₆F₄Alkyl or C₁₋₆F₄Alkoalkyl, R¹³ is C₁₋₆F₄Alkyl, C₁₋₆F₄Alkoalkyl, C_{Two-6}Alkoalkyl Le, C_{Three-6} Cycloalkyl, C_{Four-12}Cycloalkylalkyl, aryl, Aryl (C₁₋₆F₄Alkyl), heteroaryl, heteroaryl (C₁₋₆F₄Alkyl), R¹⁴ is C₁₋₆F₄Alkyl, C_{Three-6}Alkenyl, C_{Three-6}Alkynyl, C_{Three-6} Cycloalkyl, or C_{Four-12}Cycloalkylalkyl (each is independently in each case C₁₋₆Alkyl, C_{Three-6} Cycloalkyl, Halo, C₁₋₆F₄Alkoalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R^{Fifteen}, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R^{Fifteen}, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, And C₁₋₆ Alkylthio, C₁₋₆Alkylsulfanyl and C₁₋₆Alkylsulfoni Optionally substituted with 1 to 3 substituents selected from R^{Fifteen} And R¹⁶ Are independently H, C in each case C₁₋₆Alkyl, C_{Three-6} Cycloalkyl, C_{Four-12}Cycloalkylalkyl (S (O)_nR^{Fifteen} in the case of, R^{Fifteen} is not H) Aryl is phenyl or naphthyl (each radical in each case Stand up C₁₋₆Alkyl, C_{Three-6} Cycloalkyl, halo, C₁₋₆F₄Alkoalk Le, Cyano, OR^{Fifteen}, SH, S (O)_nR^{Fifteen}, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R^{Fifteen}, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, And CONR¹⁶R^{Fifteen} Any of 1 to 5 substituents selected from Has been replaced with a) Heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, Ranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, ben zothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl Or 2,3-dihydrobenzofuranyl (each group is in each case independently C₁₋₆Alkyl, C_{Three-6} Cycloalkyl, halo, C₁₋₆F₄Alkoalk Kill, Cyano, OR^{Fifteen}, SH, S (O)_nR^{Fifteen}, -COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R^{Fifteen}, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R^{Fifteen}, NR¹⁶R^{Fifteen}, And CONR¹⁶R^{Fifteen} 1 to 5 substitutions selected from Optionally substituted with a group) A heterocyclic group is a saturated or partially saturated heteroaryl (each group is independently in each case C₁₋₆Alkyl, C_{Three-6} Cycloalkyl, ha B, C₁₋₆F₄Alkoalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR^{Fifteen}, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R^{Fifteen}, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R^{Fifteen}, NR¹⁶R^{Fifteen}, And CONR¹⁶R^{Fifteen} Selected from Optionally substituted with 1 to 5 substituents) n is independently 0, 1 or 2 in each case A treatment method characterized by the fact that: 2. In the compound of the formula (1) or (2), Ar is phenyl, pyridyl, or is 2,3-dihydrobenzofuranyl, and each Ar represents 1-4 R^{Four} The method of claim 1, optionally substituted with a substituent. 3. In the compound of the formula (1) or (2), A is N and Z is CR^{Two}, Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethyl Rphenyl, R¹ And R^{Two} is methyl and R^{Three} is NR⁶R⁷ is characterized by The method of claim 1. 4. A compound of formula (1) or (2) And its isomers, its stereoisomers, or mixtures of its stereoisomers, and drugs including a pharmaceutically acceptable salt or produg thereof, in the above formula, A is N or CR^{Two}, Z is N or CR^{Two} And Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furs Nil, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzof Ranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyrani 3,4-dihydro-1,2-benzopyranyl, tetralinyl (each of A is 1-5 R^{Four} And each Ar is substituted with an unsaturated carbon atom. Joined), R is independently H, C in each case C₁₋₆F₄Alkyl, C_{Two-6}F₄Alkenyl, C_{Two-6}F₄Alkynyl, C_{Three-6} Cycloalkyl, C_{Four-12}Cycloalkyl Kill, halo, CN, C₁₋₆F₄ Selected from haloalkyl, R¹ Are independently H, C in each case C₁₋₆F₄Alkyl, C_{Two-6}F₄Alkene Le, C_{Two-6}F₄Alkynyl, halo, CN, C₁₋₆F₄Alkoalkyl, C₁₋₁₂Hydroxyalkyl, C_{Two-12}Alkoalkyl, C_{Two-6}Alkoalkyl, C_{Three-6} Cycloalkyl, C_{Four-12}Cycloalkylalkyl, NR⁶R⁷, C₁₋₆F₄Alkyl-NR⁶R⁷, NR⁸COR^{Ten}, OR¹¹, SH or S (O)_nR¹² Selected from R^{Two} is H, C₁₋₆F₄Alkyl, C_{Two-6}F₄Alkenyl, C_{Two-6}F₄Alkynyl, C_{Three-6} Cycloalkyl, C_{Four-12}Cycloalkylalkyl, C₁₋₆F₄Hydroxyalkyl, halo, CN, -NR⁶R⁷, NR⁸COR^{Ten}, NR⁸(O)_nR⁷, S (O)_nNR⁶R⁷, C₁₋₆F₄Alkoalkyl, -OR⁷, SH or S (O)_nR¹² Selected from R^{Three} is H, OR⁷, SH, S (O)_nR¹³, COR⁷, CO_{Two}R⁷, OC (O) R¹³, NR⁸COR⁷, N (COR⁷)_{Two}, NR⁸CONR¹⁶R⁷, NR⁸CO_{Two}R¹³, NR⁶R⁷, NR⁶R⁷, N (OR⁷) R⁶, CONR⁶R⁷, Aryl, heteroaryl And heterocyclic groups, or -C₁₋₆F₄Alkyl, C_{Two-6}F₄Alkenyl, C_{Two-6}F₄Alkynyl, C_{Three-6} Cycloalkyl, C_{Four-12}Cycloalkylalkyl, C_{Three-6} Cycloalkenyl, C_{Four-12}Cycloalkylalkyl Or C₆₋₁₄Cycloalkenylalkyl (each group is independently C₁₋₆Alkyl, C_{Three-6} Cycloalkyl, halo, C₁₋₆F₄Alkoalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And hetero Optionally substituted with 1 to 3 substituents selected from cyclic groups), R^{Four} is independently C₁₋₆F₄Alkyl, C_{Two-6}F₄Alkenyl, C_{Two-6}F₄Alkyl, C_{Three-6} Cycloalkyl, C_{Four-12}Cycloalkylalkyl, NO_{Two}, Ha B, CN, C₁₋₆F₄Alkoalkyl, NR⁶R⁷, NR⁸COR⁷, NR⁸CO_{Two}R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO (NOR⁶) R⁷, CO_{Two}R⁷, Or S (O)_nR⁷ (C₁₋₆F₄Alkyl, C_{Two-6}F₄Alkenyl, C_{Two-6}F₄Alkynyl, C_{Three-6} Cycloalkyl And C_{Four-12}Cycloalkylalkyl in each case independently C₁₋₆F₄Alkyl, NO_{Two}, Halo, CN, NR⁶R⁷, NR⁸COR⁷, NR⁸CO_{Two}R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO (NOR⁶) R⁷, Or S (O)_nR⁷ Optionally substituted with 1 to 3 substituents selected from Has been selected), R⁶ And R⁷, R⁶ And R⁷ Are, independently, in each case, H, -C₁₋₆F₄Alkyl, C_{Three-6}Alkenyl, C_{Three-6}Alkynyl, haloge C with 1 to 10 atoms C₁₋₆F₄Alkoalkyl, C_{Two-6}Alkoalkyl, C_{Three-6} Cycloalkyl, C_{Four-12}Cycloalkylalkyl, C_{Three-6} Cycloalkenyl or C₆₋₁₄Cycloalkenylalkyl (each group is in each case independently C₁₋₆Alkyl, C_{Three-6} Cycloalkyl, halo, C₁₋₆F₄Alkoalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁₋₆F₄Alkyl), heteroaryl, heteroaryl Le (C₁₋₆F₄Alkyl), a heterocyclic group or a heterocyclic (C₁₋₆F₄Alkyl) Selected or Alternatively, NR⁶R⁷ And NR⁶R⁷ Are independently piperidine, pyrrolidine, Perazine, N-methylpiperazine, morpholine or thiomorpholine (each is from 1 to 3 C₁₋₆F₄ Optionally substituted with an alkyl group), R⁶ is independently H or C in each case C₁₋₆F₄ Selected from alkyl, R⁹ And R^{Ten} Are independently H, C in each case C₁₋₆F₄Alkyl, or C_{Three-6} Selected from cycloalkyl, R¹¹ is H, C₁₋₆F₄Alkyl, C₁₋₆F₄Alkoalkyl or C_{Three-6} Cycloa Selected from Luqil, R¹² is C₁₋₆F₄Alkyl or C₁₋₆F₄Alkoalkyl, R¹³ is C₁₋₆F₄Alkyl, C₁₋₆F₄Alkoalkyl, C_{Two-6}Alkoalkyl Le, C_{Three-6} Cycloalkyl, C_{Four-12}Cycloalkylalkyl, aryl, Aryl (C₁₋₆F₄Alkyl), heteroaryl, heteroaryl (C₁₋₆F₄Alkyl), R¹⁴ is C₁₋₆F₄Alkyl, C_{Three-6}Alkenyl, C_{Three-6}Alkynyl, C_{Three-6} Cycloalkyl, or C_{Four-12}Cycloalkylalkyl (each is independently in each case C₁₋₆Alkyl, C_{Three-6} Cycloalkyl, Halo, C₁₋₆F₄Alkoalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R^{Fifteen}, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R^{Fifteen}, NR¹⁶R^{Fifteen}, And CONR¹⁶R^{Fifteen} Any of 1 to 5 substituents selected from Has been replaced by) Heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, Ranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, ben zothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl Or 2,3-dihydrobenzofuranyl (each group is in each case independently C₁₋₆Alkyl, C_{Three-6} Cycloalkyl, halo, C₁₋₆F₄Alkoalk Kill, Cyano, OR^{Fifteen}, SH, S (O)_nR^{Fifteen}, -COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R^{Fifteen}, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R^{Fifteen}, NR¹⁶R^{Fifteen}, And CONR¹⁶R^{Fifteen}

NR¹⁶R^{Fifteen}, And CONR¹⁶R^{Fifteen} With 1 to 5 substituents selected from Arbitrarily substituted) A heterocyclic group is a saturated or partially saturated heteroaryl (each group is independently in each case C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Halalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR^{Fifteen}, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R^{Fifteen}, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R^{Fifteen}, NR¹⁶R^{Fifteen}, And CONR¹⁶R^{Fifteen} Selected from Optionally substituted with 1 to 5 substituents) n is independently 0, 1 or 2 in each case; However, (1) A is N, Z is CR^{Two}, R^{Two} is H, R^{Three} is -OR⁷ or -OCOR¹³, and R⁷ is H, then R¹ is neither H, OH nor SH, (2) A is N and Z is CR^{Two}, R¹ is CH_{Three} or C_{Two}H_{Five}, R^{Two} is H, and R^{Three} is OH, H, CH_{Three}, C_{Two}H_{Five}, C₆H_{Five}, N-C_{Three}H₇, I-C_{Three}H₇, SH, SCH_{Three}, N-HC_{Four}H₉, Or N (C_{Two}H_{Five})_{Two} Where Ar is phenyl and m-CH_{Three}-Fe Not any of nil, (3) A is N, Z is CR^{Two}, R^{Two} is H, and Ar is pyridyl, pyrimidinyl or is pyrazinyl, and R^{Three} is NR^{6a}R^{7a} in the case of ^{6a} and R^{7a} is H and A Neither of Luqui, (4) A is N, Z is CR^{Two}, And R^{Two} is SO_{Two}NR⁶R⁷ in the case of ^{Three} Are OH and Neither SH nor SH (5) A is CR and Z is CR^{Two} in the case of ^{Two} is -NR⁶SO_{Two}R⁷ And -SO_{Two}NR⁶R⁷ Neither of (6) A is N, Z is CR^{Two} And R^{Two} is -NR⁶SO_{Two}R⁷ or -SO_{Two}NR⁶R⁷ of If R^{Three} is neither OH nor SH, (7) A is N, Z is CR^{Two}, R¹ is methyl or ethyl, R^{Two} is H, and R^{Three} is H, OH, CH_{Three}, C_{Two}H_{Five}, C₆H_{Five}, N-C_{Three}H₇, Iso-C_{Three}H₇, SH, SCH_{Three}, NH (N-C_{Four}H₉) Or N (C_{Two}H_{Five})_{Two} Where Ar is unsubstituted phenyl Nor m-methylphenyl, (8) A is CR, Z is CR^{Two}, R^{Two} is H, phenyl or alkyl, R^{Three} is NR⁶C OR⁷ And when Ar is phenyl or phenyl substituted with phenylthio, R⁷ is aryl, aryl (C₁-C_{Four}Alkyl), heteroaryl, heteroaryl (C₁-C_{Four}Alkyl), heterocyclic groups and heterocycles (C₁-C_{Four}Alkyl) Neither (9) A is CR, Z is CR^{Two}, R^{Two} is H or alkyl, Ar is phenyl, and R^{Three} is SR¹⁰ or NR^{6a}R^{7a} in the case of ¹³ is aryl and heteroaryl R^{6a} And R^{7a} is neither H nor aryl, and is (10) A is CH, Z is CR^{Two}, R¹ is OR¹¹, R^{Two} is H, R^{Three} is OR⁷ And R⁷ And R¹¹ Are H, Ar is phenyl, p-Br-phenyl, p-C₁-phenyl, p-NHCOCH_{Three}-Phenyl, p-CH_{Three}-Phenyl, pyridyl And neither naphthyl, (11) A is CH, Z is CR^{Two}, R^{Two} is H, Ar is unsubstituted phenyl, and R^{Three} But CH_{Three}-C_{Two}H_{Five}-CF_{Three} or C₆H_{Four} in the case of F, R¹ is CF_{Three} And C_{Two}F_{Five} Nozomi Not so (12) A is CR, R is H, Z is CR^{Two}, R^{Two} is OH, and R¹ And R^{Three} is H Where Ar is not phenyl, (13) A is CR, R is H, Z is CR^{Two}, R^{Two} is OH or NH_{Two}, R¹ And R^{Three} is CH_{Three} in the case of Ar is 4-phenyl-3-cyano-2-aminopyrido-2- Not I A compound comprising: 5. (1) A is N, R¹ is H, C₁-C_{Four}Alkyl, halo, CN, C₁-C₁₂H_{Two}Hydroxyalkyl, C₁-C_{Four}Alkoxyalkyl or SO_{Two}(C₁-C_{Four}Alkyl), R^{Three} is NR^{6a}R^{7a} in R^{6a} is unsubstituted C₁-C_{Four} in the case of alkyl, R^{7a} is Fe Nil, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl and C_{Three}-C₆Shi (2) A is N, R¹ is H, C₁-C_{Four}Alkyl, Halo, CN, C₁-C₁₂Hydroxyalkyl, C₁-C_{Four}Alkoxyalkyl or is SO_{Two}(C₁-C_{Four}Alkyl), R^{Three} is NR^{6a}R^{7a} in R^{7a} is unsubstituted C₁-C_{Four}Al R for k^{6a} is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, Drift and C_{Three}-C₆With the additional condition of not being a cycloalkyl The compound according to claim 4, an isomer thereof, and a stereoisomer thereof, Or a mixture of its stereoisomers, and a pharmaceutically acceptable salt or Prodrug body. 6. Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, Each one to four R^{Four} Characterized by being optionally substituted with a substituent 5. The compound according to claim 4, and its isomer, its stereoisomer, or its stereoisomer Mixtures of the compounds, and pharmaceutically acceptable salts or prodrugs thereof. 7. A is N, Z is CR^{Two}, Ar is 2,4-dichlorophenyl, 2,4-dimethyl Phenyl or 2,4,6-trimethylphenyl, R¹ And R^{Two} is CH_{Three} And R^{Three} is NR^{6a}R^{7a}. The compound according to claim 6, wherein the compound is an isomer thereof, its stereoisomers, or a mixture of its stereoisomers, and pharmaceutically acceptable A salt or prodrug thereof. 8. A pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 4. A pharmaceutical composition comprising: 9. A pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 6. A pharmaceutical composition comprising: 10. A pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 7. A pharmaceutical composition comprising a substance. 11. The compound according to claim 4, wherein A is N, and an isomer thereof, its stereoisomers, or a mixture of its stereoisomers, and pharmaceutically acceptable A salt or prodrug thereof. 12. The compound of the formula (2) according to claim 11, its isomer, its stereoisomer Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 13. Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, And each Ar is 1 to 4 R^{Four} Characterized by being optionally substituted with a substituent 13. The compound according to claim 12, and its isomers, its stereoisomers, or its compounds. Mixtures of isomers, and pharmaceutically acceptable salts or prodrugs thereof. 14. R^{Three} is NR^{6a}R^{7a} or OR⁷13. The method according to claim 12, wherein A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. 15. Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl; And each Ar is 1 to 4 R^{Four} Optionally substituted with substituents, ^{Three} is NR^{6a}R^{7a} or OR⁷13. The compound according to claim 12, which is, its stereoisomers, or a mixture of its stereoisomers, and pharmaceutically acceptable Functional salts or prodrugs thereof. 16. Z is CR^{Two} The compound of formula (1) according to claim 11, wherein And its isomers, its stereoisomers, or mixtures of its stereoisomers, and drugs A pharmaceutically acceptable salt or prodrug thereof. 17. Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl; And each Ar is 1 to 4 R^{Four} Characterized by being optionally substituted with a substituent 17. The compound according to claim 16 and its isomers, its stereoisomers, or its erects. Mixtures of isomers, and pharmaceutically acceptable salts or prodrugs thereof. 18. R^{Three} is NR^{6a}R^{7a} or OR⁷ The method according to claim 16, wherein A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. 19. A compound according to claim 18, and its isomer, its stereoisomer, or its compound. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a} independently -4, -C₁-C_{Ten}Alkyl, C_{Three}-C_{Ten}Alkenyl, C_{Three}-C_{Ten}Alkynyl, haloge C with 1 to 10 atoms, C₁-C_{Ten}Halalkyl, C_{Two}-C₆Alkoxyalkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl, C_{Five}-C_{Ten}Cycloalkenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Halalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Five}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups). Aryl, aryl (C₁-C_{Four}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{Four}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{Four}Alkyl) Selected, R^{7a} Are, independently, in each case, -H, -C_{Five}-C_{Ten}Alkyl, C_{Three}-C_{Ten}Alkenyl, C_{Three}-C_{Ten}Alkynyl, haloge C with 1 to 10 atoms, C₁-C_{Ten}Halalkyl, C_{Two}-C₆Alkoxyalkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl, C_{Five}-C_{Ten}Cycloalkenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Halalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Five}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups). Aryl, aryl (C₁-C_{Four}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{Four}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{Four}Alkyl) Selected or Alternatively, NR^{6b}R^{7b} And NR^{6b}R^{7b} is independently piperidine, pyrrolidine, pipe Razine, N-methylpiperazine, morpholine or thiomorpholine (each The group is 1 to 3 C₁-C_{Four} (Optionally substituted with an alkyl group) The compound according to claim 15, an isomer thereof, and a stereoisomer thereof, Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 20. A compound according to claim 18, and its isomer, its stereoisomer, or its compound. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a} And R^{7a} Are the same, -C₁-C_{Four}Alkyl or C_{Three}-C₆Cycloalkyl (each group is in this case, independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Halalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, -COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Five}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), and -Selected from aryl or heteroaryl The compound according to claim 15, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 21. A compound according to claim 18, and its isomer, its stereoisomer, or its compound. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6b} But, -H, -C₁-C_{Ten}Alkyl, C_{Three}-C_{Ten}Alkenyl, C_{Three}-C_{Ten}Alkynyl, haloge C with 1 to 10 atoms, C₁-C_{Ten}Halalkyl, C_{Two}-C₆Alkoxyalkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl, C_{Five}-C_{Ten}Cycloalkenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Halalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}

NR⁸CONR¹⁶R¹⁵, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁-C_{FOUR}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{FOUR}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{FOUR}Alkyl) Selected, R^{7a}But, -C₁-C_{FOUR}Alkyl and in each case independently C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen} 1 to 3 positions selected from, aryl, heteroaryl and heterocyclic groups C optionally substituted with a substituent₁-C_{FOUR}Is alkyl The compound according to claim 18, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 22. A compound according to claim 18, and its isomer, its stereoisomer, or its compound. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}And R^{7a}One of them is -C_{THREE}-C₆Cycloalkyl (each C_{THREE}-C₆Cycloalkyl is independently in the case of: C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), -Aryl, -Heteroaryl or -A heterocyclic group, selected from R^{6a}And R^{7a}Is an unsubstituted C₁-C_{FOUR}Is alkyl The compound according to claim 18, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 23. R^{6a}And R^{7a}Is independently H or C₁-C_{TEN}Alkyl, each R^{6a} C₁-C_{TEN} The alkyl is in each case independently C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, 1-3 substituted groups selected from aryl, heteroaryl and heterocyclic groups 20. The compound according to claim 18, which is optionally substituted with a group. Isomers, their stereoisomers, or mixtures of their stereoisomers, and pharmaceutically An acceptable salt or prodrug thereof. 24. Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, And each has 1 to 4 R^{FOUR}Optionally substituted with substituents, Three⁹Is NR⁸R^{7a}Also is OR⁷The compound according to claim 16, and isomers thereof, The stereoisomer, or a mixture of the stereoisomers, and a pharmaceutically acceptable salt or prodrug form thereof. 25. 25. The compound according to claim 24 and isomers thereof, stereoisomers thereof, or compounds thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}Independently -H, -C₁-C_{TEN}Alkyl, C_{THREE}-C_{TEN}Alkenyl, C_{THREE}-C_{TEN}Alkynyl, haloge C with 1 to 10 atoms; C_{TEN}Haloalkyl, C_{TWO}-C₆Alkoxyalkyl, C_{THREE}-C₆Cycloalkyl, C_{FOUR}-C₁₂Cycloalkylalkyl, C_{FIVE}-C_{TEN}Cycloa Lucenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R¹⁵, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁-C_{FOUR}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{FOUR}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{FOUR}Alkyl) Selected, R^{7a}Are, independently, in each case, -H, -C_{FIVE}-C_{TEN}Alkyl, C_{THREE}-C_{TEN}Alkenyl, C_{THREE}-C_{TEN}Alkynyl, haloge C with 1 to 10 atoms; C_{TEN}Haloalkyl, C_{TWO}-C₆Alkoxyalkyl, C_{THREE}-C₆Cycloalkyl, C_{FOUR}-C₁₂Cycloalkylalkyl, C_{FIVE}-C_{TEN}Cycloa Lucenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R¹⁵, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aily Optionally with 1 to 3 substituents selected from phenyl, heteroaryl and heterocyclic groups. Has been replaced), Aryl, aryl (C₁-C_{FOUR}Alkyl), heteroaryl, heteroaryl Le (C₁-C₄ alkyl), a heterocyclic group or a heterocyclic (C₁-C_{FOUR}Alkyl) Selected or Alternatively, NR⁸R⁷And NR⁸R^{7a}Is independently piperidine, pyrrolidine, pipe Razine, N-methylpiperazine, morpholine or thiomorpholine (each The group is 1 to 3 C₁-C_{FOUR}Optionally substituted with an alkyl group) The compound according to claim 24, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 26. 25. The compound according to claim 24 and isomers thereof, stereoisomers thereof, or compounds thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}And R^{7a}Are the same, -C₁-C_{FOUR}Alkyl or C_{THREE}-C₆Cycloalkyl (each group is in this case, independently C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R¹⁵, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups) And -Selected from aryl or heteroaryl The compound according to claim 24, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 27. 25. The compound according to claim 24 and isomers thereof, stereoisomers thereof, or compounds thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}And R^{7a}Are the same, -C₁-C_{FOUR}Alkyl (each C₁-C_{FOUR}Alkyl is in each case independent Then C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}Haloalkyl, Cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R¹⁵, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl and heterocyclic groups Arbitrarily substituted with 1 to 3 substituents selected from Do 25. The compound according to claim 24, an isomer thereof, a stereoisomer thereof, or a stereoisomer thereof. Mixtures of isomers, and pharmaceutically acceptable salts or prodrugs thereof. 28. 25. The compound according to claim 24 and isomers thereof, stereoisomers thereof, or compounds thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}Is -H, -C₁-C_{TEN}Alkyl, C_{THREE}-C_{TEN}Alkenyl, C_{THREE}-C_{TEN}Alkynyl, haloge C with 1 to 10 atoms; C_{TEN}Haloalkyl, C_{TWO}-C₆Alkoxyalkyl, C_{THREE}-C₆Cycloalkyl, C_{FOUR}-C₁₂Cycloalkylalkyl, C_{FIVE}-C_{TEN}Cycloa Lucenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R¹⁵, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁-C_{FOUR}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{FOUR}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{FOUR}Alkyl) Selected, R^{7a}Is -C₁-C_{FOUR}Alkyl and in each case independently C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen} 1 to 3 positions selected from, aryl, heteroaryl and heterocyclic groups C optionally substituted with a substituent₁-C_{FOUR}Is alkyl The compound according to claim 24, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 29. 25. The compound according to claim 24 and isomers thereof, stereoisomers thereof, or compounds thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}And R^{7a}One of them is -C_{THREE}-C₆Cycloalkyl (each C_{THREE}-C₆Cycloalkyl is independently C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}C Low alkyl, cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, O C (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl and multiple Optionally substituted with 1 to 3 substituents selected from cyclic groups), -Aryl, -Heteroaryl or -A heterocyclic group, selected from R^{6a}And R^{7a}Is an unsubstituted C₁-C_{FOUR}Is alkyl The compound according to claim 24, an isomer thereof, and a stereoisomer thereof. , Or a mixture of its stereoisomers, and a pharmaceutically acceptable salt or Drag body. 30. R^{6a}And R^{7a}Is independently H or C₁-C_{TEN}Alkyl, each R^{6a} C₁-C_{TEN} The alkyl is in each case independently C₁-C₆Alkyl, C_{THREE}-C₆Cycloalkyl, halo, C₁-C_{FOUR}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)₁R¹³, COR^{Fifteen}, CO_{TWO}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{TWO}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{TWO}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, 1-3 substituted groups selected from aryl, heteroaryl and heterocyclic groups 25. The compound according to claim 24, which is optionally substituted with a group. Isomers, their stereoisomers, or mixtures of their stereoisomers, and pharmaceutically An acceptable salt or prodrug thereof. 31. 17. The compound according to claim 16, and its isomer, its stereoisomer, or its compound. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body -Ar is 1 to 4 R^{FOUR}Phenyl,

p-aryl or phenyl optionally substituted with a substituent 2,3-dihydrobenzofuran-7-yl, R^{6a} is NR^{6a}R^{7a} or OR^{7a} and -R³ and R^{7a} are independently H, C_{1-C4}Alkyl, C₃₋₇Cycloalkyl, C_{4-Four}Cycloalkyl, C_{Ten}. Selected from cycloalkylalkyl The compound according to claim 16, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 32. The compound according to claim 31, and an isomer, a stereoisomer, or a compound thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}Independently -H, -C_{1-C4}Alkyl, C_{Three-CTen}Alkenyl, C_{Three-CTen}Alkynyl, haloge C with 1 to 10 atoms, C_{Ten}-Haloalkyl, C_{Two-C8}Alkoxyalkyl, C_{Three-C6}Cycloalkyl, C_{Four-C12}Cycloalkylalkyl, C_{Five-CTen}Cyclo Lucenyl or C_{6-C14}Cycloalkenylalkyl (each group is in each case independently C_{1-C6}Alkyl, C_{Three-C6}Cycloalkyl, halo, C_{1-C4}Alkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{1 Five}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C_{1-C4}Alkyl), heteroaryl, heteroaryl (C_{1-C4}Alkyl), a heterocyclic group or a heterocyclic (C_{1-C4}Alkyl) And R^{7a}is -H, -C_{Five-CTen}Alkyl, C_{Three-CTen}Alkenyl, C_{Three-CTen}Alkynyl, haloge C with 1 to 10 atoms, C_{Ten}Haloalkyl, C_{Two-C8}Alkoxyalkyl, C_{Three-C6}Cycloalkyl, C_{Four-C12}Cycloalkylalkyl, C_{Five-CTen}Cyclo Lucenyl or C_{6-C14}Cycloalkenylalkyl (each group is in each case independently C_{1-C6}Alkyl, C_{Three-C6}Cycloalkyl, halo, C_{1-C4}Alkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{1 Five}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C_{1-C4}Alkyl), heteroaryl, heteroaryl Le (C_{1-C4}Alkyl), a heterocyclic group or a heterocyclic (C_{1-C4}Alkyl) Selected or Alternatively, NR^{6a}R^{7a}And NR^{6a}R^{7a}Are independently piperidine, pyrrolidine, Perazine, N-methylpiperazine, morpholine or thiomorpholine (each is from 1 to 3 C_{1-C4}Optionally substituted with an alkyl group) is there The compound according to claim 31, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 33. The compound according to claim 31, and an isomer, a stereoisomer, or a compound thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}And R^{7a}Are the same, -C_{1-C4}Alkyl or C_{Three-C6}Cycloalkyl (each group is in this case, independently C_{1-C6}Alkyl, C_{Three-C6}Cycloalkyl, halo, C_{1-C4}Alkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{1 Five}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups) And -Selected from aryl or heteroaryl The compound according to claim 31, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 34. The compound according to claim 31, and an isomer, a stereoisomer, or a compound thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}And R^{7a}Are the same, -C_{1-C4}Alkyl (each C_{1-C4}Alkyl is in each case independent Then C_{1-C6}Alkyl, C_{Three-C6}Cycloalkyl, halo, C_{1-C4}Alkyl, Cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{1 Five}, NR⁶CO_{Two}R^{1 Three}, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl and heterocyclic groups Arbitrarily substituted with 1 to 3 substituents selected from The compound according to claim 31, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 35. The compound according to claim 31, and an isomer, a stereoisomer, or a compound thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}Is -H, -C_{1-C4}Alkyl, C_{Three-C4}Alkenyl, C_{Three-C4}Alkynyl, haloge C with 1 to 10 atoms, C_{Ten}Haloalkyl, C_{Two-C8}Alkoxyalkyl, C_{Three-C6}Cycloalkyl, C_{Four-C12}Cycloalkylalkyl, C_{Five-CTen}Cyclo Lucenyl or C_{6-C14}Cycloalkenylalkyl (each group is in each case independently C_{1-C6}Alkyl, C_{Three-C6}Cycloalkyl, halo, C_{1-C4}Alkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{1 Five}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C_{1-C4}Alkyl), heteroaryl, heteroaryl Le (C_{1-C4}Alkyl), a heterocyclic group or a heterocyclic (C_{1-C4}Alkyl) Selected, R^{7a}is -C_{1-C4}Alkyl and in each case independently C_{1-C6}Alkyl, C_{Three-C6}Cycloalkyl, halo, C_{1-C4}Alkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{1 Five}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, 1 to 3 positions selected from, aryl, heteroaryl and heterocyclic groups C optionally substituted with a substituent; C_{Four}is alkyl The compound according to claim 31, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 36. The compound according to claim 31, and an isomer, a stereoisomer, or a compound thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body R^{6a}And R^{7a}One of them is -C_{Three-C6}Cycloalkyl (each C_{Three-C6}Cycloalkyl is independently in the case of C_{1-C6}Alkyl, C_{Three-C6}Cycloalkyl, halo, C_{1-C4}Alkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{1 Five}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl and Optionally substituted with 1 to 3 substituents selected from heterocyclic groups). -Aryl, -Heteroaryl or -A heterocyclic group, selected from R^{6a}And R^{7a}is an unsubstituted C_{1-C4}is alkyl The compound according to claim 31, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or Lodrug body. 37. R^{6a}And R^{7a}is independently H or C_{1-C4}Alkyl, each R^{6a}Or C_{1-C4}The alkyl is in each case independently C_{1-C6}Alkyl, C_{Three-C6}Cycloalkyl, halo, C_{1-C4}Alkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{1 Five}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, 1-3 substituted groups selected from aryl, heteroaryl and heterocyclic groups 32. The compound according to claim 31, which is optionally substituted with a group, isomers, their stereoisomers, or mixtures of their stereoisomers, and pharmaceutically acceptable salt or produg thereof. 38. The compound of claim 31, wherein the compound is of formula (50): And its isomers, its stereoisomers, or mixtures of its stereoisomers, and drugs A pharmaceutically acceptable salt or produg thereof, R^{Threets}is -NHCH (n-Pr)_{Two}, R^{4a}is Cl, R^{4b}is H, R^{4c}is Cl, R^{4d}is H And R^{4e}A compound of formula (50) wherein is H R^{Threets}is -N (Et) (n-Bu),

[illegible]

claim 31, wherein the compound is zolo-1,3, triazine. And its isomers, its stereoisomers, or a mixture of its stereoisomers, and A pharmaceutically acceptable salt or prodrug thereof. 46. The compound is 4- (bis- (2-methoxyethyl) amino) -2,7- Dimethyl-8- (2,6-dimethyl-4-methoxyphenyl)-1,5-a) 32. Pyrazolo-1,3,5-triazine. A compound and isomers thereof, stereoisomers thereof, or a mixture of stereoisomers thereof. And pharmaceutically acceptable salts or prodrugs thereof. 41. The compound according to claim 4, wherein A is CR, isomers thereof, and stereoisomers thereof. Or a mixture of its stereoisomers, and a pharmaceutically acceptable salt or prodrug body. 42. 42. The compound of the formula (2) according to claim 41, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or prodrug body. 43. Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, And each Ar is 1 to 4 R^{Four}Characterized by being optionally substituted with a substituent 43. The compound according to claim 42 and isomers thereof, stereoisomers thereof, or Mixtures of stereoisomers, and pharmaceutically acceptable salts or prodrugs thereof. 44. R^{Three} is NR^{6a7a}OR⁷43. The method according to claim 42, wherein A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. 45. Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl; And each Ar is 1 to 4 R^{Four}Optionally substituted with substituents, ^{Three} is NR^{6a7a}OR⁷43. The compound according to claim 42, wherein Sex, its stereoisomer, or a mixture of its stereoisomers, and pharmaceutically acceptable Possible salts or prodrugs thereof. 46. Z is CR^{Two}42. The compound of formula (1) according to claim 41, wherein And its isomers, its stereoisomers, or mixtures of its stereoisomers, and drugs A pharmaceutically acceptable salt or prodrug thereof. 47. Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl; And each Ar is 1 to 4 R^{Four}Characterized by being optionally substituted with a substituent 47. The compound according to claim 45 and its isomers, its stereoisomers, or its Standing Mixtures of isomers, and pharmaceutically acceptable salts or prodrugs thereof. 48. R^{Three} is NR^{6a7a}OR⁷The method according to claim 46, wherein A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. 49. Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl; And each Ar is 1 to 4 R^{Four}Optionally substituted with substituents, ^{Three} is NR^{6a7a}OR⁷47. The compound according to claim 46, wherein Sex, its stereoisomer, or a mixture of its stereoisomers, and pharmaceutically acceptable Possible salts or prodrugs thereof. 50. R^{6a}And R^{7a}is independently H or C₁₋₁₀TenAlkyl, and Each C₁₋₁₀TenThe alkyl is in each case independently C₁₋₆Alkyl, C_{Three-6}Cycloalkyl, halo, C₁₋₆FourHaloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR^{6a}COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR^{6a}CONR¹⁶R^{Fifteen}, NR^{6a}CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}1 to 3 selected from aryl, heteroaryl and heterocyclic groups 50. The compound according to claim 49, which is optionally substituted with a substituent. Isomers, their stereoisomers, or mixtures of their stereoisomers, and pharmaceutically An acceptable salt or prodrug thereof. 51. 47. The compound according to claim 45 and isomers thereof, stereoisomers thereof, or compounds thereof. Mixtures of the stereoisomers of, and pharmaceutically acceptable salts or prodrugs thereof Body -Ar is 1 to 4 R^{Four}Phenyl, pyridyl or phenyl optionally substituted with a substituent 2,3-dihydrobenzofuranyl, -R^{Three}is NR^{6a7a}OR⁷or OR⁷and -R¹And R^{Two}Are independently H, C₁₋₆FourAlkyl, C_{Three-6}Cycloalkyl, C_{Four-10}TenSelected from cycloalkylalkyl The compound according to claim 46, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or prodrug body. 52. R^{6a}And R^{7a}is independently H or C₁₋₁₀TenAlkyl and Each C₁₋₁₀TenThe alkyl is in each case independently C₁₋₆Alkyl, C_{Three-6}Cycloalkyl, halo, C₁₋₆FourHaloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR^{6a}COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR^{6a}CONR¹⁶R^{Fifteen}, NR^{6a}CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}1 to 3 selected from aryl, heteroaryl and heterocyclic groups 52. The compound according to claim 51, which is optionally substituted with a substituent. Isomers, their stereoisomers, or mixtures of their stereoisomers, and pharmaceutically An acceptable salt or prodrug thereof. 53. A compound according to claim 51, wherein the compound is of the formula (51): And its isomers, its stereoisomers, or mixtures of its stereoisomers, and drugs A pharmaceutically acceptable salt or prodrug thereof, R^{Three}is -NHCH (n-Pr)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H And R^{6e}A compound of formula (51) wherein R^{Three}is -NHCH (CH_{Two}OMe)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -N (C-Pr) (CH_{Two}CH_{Two}CN), R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -NHCH (CH_{Two}OMe)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -N (C-Pr) (CH_{Two}CH_{Two}CN), R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -NHCH (Et)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -N (n-Pr) (CH_{Two}CH_{Two}CN), R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -N (n-Bu) (CH_{Two}CH_{Two}CN), R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -NHCH (n-Pr) (CH_{Two}OMe), R^{6a}is Me, R^{6b}is H, R^{6c}is H, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -NHCH (Et)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -NHCH (CH_{Two}OMe)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -NH (CH_{Two}CH_{Two}OMe) CH_{Two}OMe, R^{6a}is Me, R^{6b}is H, R^{6c}is H, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -NH (Et), R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -NHCH (n-Pr)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -NHCH (CH_{Two}OMe)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -NH (CH_{Two}CH_{Two}OMe) CH_{Two}OMe, R^{6a}is Cl, R^{6b}is H, R^{6c}is H, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -N (n-Pr) (CH_{Two}CH_{Two}CN), R^{6a}is Me, R^{6b}is H, R^{6c}is O Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is -N (Et)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Three}is (S) -NH (CH_{Two}CH_{Two}OMe) CH

(Et)₂N⁺R^{10c}Cl⁻, R^{10c}is H, R^{10c}is Cl, R^{10c}is H, R^{10c}is H R^{10c}A compound of formula (51) wherein R^{Threel}is -NHCH(Et)₂N⁺R^{10c}Me, R^{10c}is Me, R^{10c}is H, R^{10c}is Me, R^{10c}is H R^{10c}A compound of formula (51) wherein R^{Threel}is -NHCH(Et)₂N⁺R^{10c}Me, R^{10c}is H, R^{10c}is Cl, R^{10c}is H R^{10c}A compound of formula (51) wherein R^{Threel}is -NEt₂N⁺R^{10c}Me, R^{10c}is Me, R^{10c}is H, R^{10c}is OMe, R^{10c}is H and R^{10c}But A compound of formula (51) which is H, R^{Threel}is -N(P)(CH₂CH₂OH)₂ON), R^{10c}is Me, R^{10c}is H, R^{10c}is OMe, R^{10c}is H and R^{10c}A compound of formula (51) wherein 52. The compound according to claim 51, which is selected from the group consisting of isomers, their stereoisomers, or mixtures of their stereoisomers, and pharmaceutically acceptable salt or prodrug thereof. 54. The compound is 7-(3-pentylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine 52. The compound according to claim 51, an isomer thereof, and a stereoisomer thereof. Or a mixture of its stereoisomers, and pharmaceutically acceptable salts or is a prodrug. 55. The compound is 7-(diethylamino)-2,5-dimethyl-3-(2-Methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine The compound according to claim 51 and isomers thereof, stereoisomers thereof, Or a mixture of its stereoisomers, and a pharmaceutically acceptable salt or Drug body. 56. The compound is 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-Dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]- 52. The compound according to claim 51, which is pyrazolopyrimidine. Isomers, their stereoisomers, or mixtures of their stereoisomers, and pharmaceutically acceptable salt or prodrug thereof. 57. A pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 4. A pharmaceutical composition comprising a substance. 58. 25. A compound according to claim 24, wherein the carrier is a pharmaceutically acceptable carrier and a therapeutically effective amount. A pharmaceutical composition comprising the compound. 59. A pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 38. A pharmaceutical composition comprising the compound. 60. A pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 39. A pharmaceutical composition comprising the compound. 61. A pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 40. A pharmaceutical composition comprising the compound. 62. 54. A compound according to claim 53, wherein the carrier is a pharmaceutically acceptable carrier and a therapeutically effective amount. A pharmaceutical composition comprising the compound. 63. 55. A compound according to claim 54, wherein the agent is a pharmaceutically acceptable carrier and a therapeutically effective amount. A pharmaceutical composition comprising the compound. 64. 56. The compound of claim 55, wherein the carrier is a pharmaceutically acceptable carrier and a therapeutically effective amount. A pharmaceutical composition comprising the compound. 65. 57. A compound as claimed in claim 56 wherein the carrier is a pharmaceutically acceptable carrier and a therapeutically effective amount. A pharmaceutical composition comprising the compound. 66. Administering a therapeutically effective amount of the compound of claim 4 to a mammal. Affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder. Supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa or Other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular Disease or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, bleeding Sexual stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcer, muscle Treatment of amyotrophic lateral sclerosis, hypoglycemia, or a disorder by antagonizing CRF including or impaired by CRF-induced or facilitated Treatment in mammals, including but not limited to disorders. 67. A method for administering a therapeutically effective amount of a compound according to claim 24 to a mammal. Symptomatic affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder Harm, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa Are other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular Tube or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, Blood stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcers, Treatment of amyotrophic lateral sclerosis, hypoglycemia, or disorders due to antagonism of CRF including or impaired by or induced by CRF Treatment in mammals, including but not limited to disorders. 68. 39. A method comprising administering to a mammal a therapeutically effective amount of a compound according to claim 38. Symptomatic affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder Harm, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa Are other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular Tube or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, Blood stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcers, Treatment of amyotrophic lateral sclerosis, hypoglycemia, or disorders due to antagonism of CRF including or impaired by or induced by CRF Treatment in mammals, including but not limited to disorders. 69. A method comprising administering to a mammal a therapeutically effective amount of a compound of claim 39. Symptomatic affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder Harm, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa Are other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular Tube or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, Blood stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcers, Treatment of amyotrophic lateral sclerosis, hypoglycemia, or disorders due to antagonism of CRF including or impaired by or induced by CRF Treatment in mammals, including but not limited to disorders. 70. A method for administering a therapeutically effective amount of a compound according to claim 40 to a mammal. Symptomatic affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder Harm, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa Are other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular Tube or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, Blood stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcers, Treatment of amyotrophic lateral sclerosis, hypoglycemia, or disorders due to antagonism of CRF including or impaired by or induced by CRF Treatment in mammals, including but not limited to disorders. 71. 55. A method comprising administering to a mammal a therapeutically effective amount of a compound according to claim 53. Symptomatic affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder Harm, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa Are other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular Tube or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, Blood stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcers, Treatment of amyotrophic lateral sclerosis, hypoglycemia, or disorders due to antagonism of CRF including or impaired by or induced by CRF Treatment in mammals, including but not limited to disorders. 72. 55. A method comprising administering to a mammal a therapeutically effective amount of a compound according to claim 54. Symptomatic affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder Harm, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa Are other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular Tube or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, Blood stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcers, Treatment of amyotrophic lateral sclerosis, hypoglycemia, or disorders due to antagonism of CRF including or impaired by or induced by CRF So Treatment in mammals, including but not limited to disorders. 73. 55. A method comprising administering to a mammal a therapeutically effective amount of a compound according to claim 55. Symptomatic affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder Harm, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa Are other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular Tube or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, Blood stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcers, Treatment of amyotrophic lateral sclerosis, hypoglycemia, or disorders due to antagonism of CRF including or impaired by or induced by CRF Treatment in mammals, including but not limited to disorders. 74. 55. A method for administering to a mammal a therapeutically effective amount of a compound according to claim 56. Symptomatic affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder Harm, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, anorexia nervosa Are other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular Tube or heart disease, fertility problems, human immunodeficiency virus (HIV) infection, Blood stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke, ulcers, Treatment of amyotrophic lateral sclerosis, hypoglycemia, or disorders due to antagonism of CRF including or impaired by or induced by CRF Treatment in mammals, including but not limited to disorders.

Description

translated from Japanese

DETAILED DESCRIPTION OF THE INVENTION	Azolo-triazines and azolopyrimidines	Field of the invention
<p>The present invention relates to certain [1,5-a]-pyrazolo-1,3,5-triazines, [1,5-a]-1,2,3-triazolo-1,3,5-triazines, [1, 5-a]-Pyrazolo-pyrimidines and [1,5-a]-1,2,3-tria Major depression, anxiety-related illness and post-traumatic illness by administration of zolo-pyrimidines Psychiatric disorders and neurology, including stress disorders, supranuclear palsy and eating disorders Treatment of immunological disorders, immunological disorders, cardiovascular or cardiac disorders, and psychopathology Treatment of colon irritability associated with</p>		

biological disorders and stress. **Background of the invention** Adrenocorticotropin-releasing factor (hereinafter referred to as CRF) contains 41 amino acids A peptide consisting of pro-opiomelanocortin (POM) from the anterior pituitary gland C) is a major physiological regulator of peptide secretion from J. Rivier et al., Proc. at Acad. Sci. (USA), 80, 4851, 1983; W.C. Vale et al., Science 213, 1394, 1981). In addition to the endocrine role in the pituitary gland, CRF The immunohistochemical localization of F has revealed that this hormone is widely distributed outside the hypothalamus, with the role of neurotransmitters or neuromodulators in the brain Produce a wide range of autonomic, electrophysiological and behavioral effects in harmony (W. Vale et al., Rec. Prog. Horm. Res. 39, 245, 1983; G.E.K. oob, Persp. Behav. Med. 2, 39, 1985; E.B. De Souza et al. Neuro sci. 5, 3189, 1985). CRF is physiological, psychological and immunological Evidence also plays a key role in integrating the immune system response to strategic stressors Ves (J.E. Blalock, Physiological Reviews, Vol. 69, page 1, 1989; J.E.M. orley, Life Sci. 41, 527, 1987). Clinical data show that CRF includes psychiatry including depression, anxiety-related diseases and eating disorders Provides evidence for a role in neurological disorders and neurological disorders. Alzheimer's disease, Parkinson's disease, Huntington's chorea, progressive supranuclear palsy and muscle atrophy Diseases associated with dysfunction of CRF neurons of the central nervous system, such as lateral sclerosis The role of CRF has also been postulated in the etiology and pathophysiology of E.B.D. e Souza, Hosp. Practice, vol. 23, p. 59, 1988). Cerebral cerebrospinal fluid C The CRF concentration in SF is significantly increased (C.B. Nemeroff et al., Science, 226, 1, 342, 1984; C.M. Banki et al., Am.J. Psychiatry, 144 volumes, 873 pages, 1987 years; R.D. France et al., Biol. Psychiatry, 28, 86, 1988; Arato and others Biol Psych latry, 25, 355, 1989). in addition, in the suicide frontal cortex CRF receptor density was also significantly reduced, consistent with CRF hypersecretion (C.B. Nemeroff et al., Arch. Gen. Psychiatry, 45, 577, 1988). Also depression in patients, corticotropin (ACTH) against CRF (administered IV) Has been observed (P.W. Gold et al., Am. J. Psychiatry, 141, 619). Page, 1984; Holsboer et al., Psychoneuroendocrinology, Volume 9, pp. 147 1984; P.W. Gold et al., New Eng. J. Med. 314, 1129, 1986). La Preclinical studies in rats and non-human primates have also shown that hypersecretion of CRF Providing further support for the hypothesis that it is involved in the symptoms seen in depression (R.M. Sapolsky, Arch. Gen. Psychiatry, 46, 1047, 1989). Tricyclic antidepressants alter CRF levels and modulate multiple CRF receptors in the brain There is some preliminary evidence that this is the case (Grigoriadis et al., Neuropsychopharmacology, Volume 2 53, 1989). The role of CRF has also been postulated in the etiology of anxiety-related diseases. CRF is Produces anxiogenic effects in animals, causing benzodiazepine / interaction between benzodiazepine anxiolytics and CRF has been shown in various behavioral anxiety models (D.R. Britton et al., Life Sci. 31, 383, 1982; C.W. Berridge and A.J. Dunn Regul. Peptides, 16, 83, 1986). Using a-helical sheep CRF (9-41), which is presumed to be a CRF receptor antagonist Preliminary studies in various behavioral cases showed that the antagonists were benzodiazepines Same as Produces an "anxiolytic-like" effects of And A.J. Dunn Horm. Behav. 21, 393 pages, 1987, Brain Research Reviews Vol. 15, p. 71, 1990). All neurochemical, endocrine and receptor binding studies Clarified the interaction between CRF and benzodiazepine anxiolytics, Provided further evidence of the involvement of CRF in patients. Chlordiazepoxide is used in the rat conflict test (K.T. Britton et al., Psychopharmacology, 86, 170 pages, 1985; K.T. Britton et al., Psychopharmacology, 94 306, 1988) and acoustic startle test (N.R. rdlow et al., Psychopharmacology, 88, 147, 1986) Weakens the 'anxiety-producing' effects of CRF. Benzodiazepine receptor antagonist (Ro15-1788) lacks behavioral activity only in the operant conflict test, but dose-dependently A benzodiazepine inverse agonist (FG7142) reverses the effects of RF on CRF (K.T. Britton et al., Psychopharmacology, 94, 306, 1988 years). Mechanisms and parts of action by which conventional anxiolytics and antidepressants produce therapeutic effects The rank remains out of estimation. However, these drugs have not been identified in the disease. Has been hypothesized to be involved in the suppression of CRF hypersecretion. Especially interested Deep is the CRF receptor antagonist (a-helix sheep C) in various behavioral cases. RF₉₋₄₁ In a preliminary study investigating the effects of benzodiazepines, (G.F.) . Koob and K.T. Britton, Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide, E.B. De Souza and C.B. Nemeroff, CRF Press, p. 221, 1990). Several publications have reported on corticotropin-releasing factor antagonist compounds and psychiatrists Their use in the treatment of biological disorders and neurological diseases is described. This Publications such as, for example, DuPont Merck PCT Application US94 / 11050, , Pfizer WO95 / 33750, Pfizer WO95 / 34563, Pfizer WO95 / 33727 and Pfizer EP 0778 277 A1. To the best of knowledge, [1,5-a]-pyrazolo-1,3,5-triazines, [1,5-a]-1,2,3-triazolo-1,3,5-triazines, [1,5-a]-pyrazolo-pyrimidines and [1,5-a]-1,2,3-triazolo-pyrimidines are useful in treating psychiatric and neurological disorders It has never been reported as a stimulating hormone releasing factor antagonist compound. Only However, there are publications that teach the use of some of these compounds for other uses. Was. For example, EP 0 269 859 (Otsuka, 1988) is represented by the following equation: In the above formula, R¹ is OH or alkanyl, R² is H, OH or SH, and R³ is H or alkyl. But Pyrazolotriazine compounds which are unsaturated heterocyclic groups, naphthyl or substituted phenyl Compounds having xanthine oxidase inhibitory activity and treating gout It is useful for medical treatment. EP 0 594 149 (Otsuka, 1994) is represented by the following equation: In the above formula, A is CH or N, R⁰ is H or alkyl, R¹ is H or alkyl, R² is H or alkyl, R³ is H or alkyl, R⁴ is H or alkyl, R⁵ is H or alkyl, R⁶ is H or alkyl, R⁷ is H or alkyl, R⁸ is H or alkyl, R⁹ is H or alkyl, R¹⁰ is H or alkyl, R¹¹ is H or alkyl, R¹² is H or alkyl, R¹³ is H or alkyl, R¹⁴ is H or alkyl, R¹⁵ is H or alkyl, R¹⁶ is H or alkyl, R¹⁷ is H or alkyl, R¹⁸ is H or alkyl, R¹⁹ is H or alkyl, R²⁰ is H or alkyl, R²¹ is H or alkyl, R²² is H or alkyl, R²³ is H or alkyl, R²⁴ is H or alkyl, R²⁵ is H or alkyl, R²⁶ is H or alkyl, R²⁷ is H or alkyl, R²⁸ is H or alkyl, R²⁹ is H or alkyl, R³⁰ is H or alkyl, R³¹ is H or alkyl, R³² is H or alkyl, R³³ is H or alkyl, R³⁴ is H or alkyl, R³⁵ is H or alkyl, R³⁶ is H or alkyl, R³⁷ is H or alkyl, R³⁸ is H or alkyl, R³⁹ is H or alkyl, R⁴⁰ is H or alkyl, R⁴¹ is H or alkyl, R⁴² is H or alkyl, R⁴³ is H or alkyl, R⁴⁴ is H or alkyl, R⁴⁵ is H or alkyl, R⁴⁶ is H or alkyl, R⁴⁷ is H or 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is H or alkyl, R⁶⁰¹ is H or alkyl, R⁶⁰² is H or alkyl, R⁶⁰³ is H or alkyl, R⁶⁰⁴ is H or alkyl, R⁶⁰⁵ is H or alkyl, R⁶⁰⁶ is H or alkyl, R⁶⁰⁷ is H or alkyl, R⁶⁰⁸ is H or alkyl, R⁶⁰⁹ is H or alkyl, R⁶¹⁰ is H or alkyl, R⁶¹¹ is H or alkyl, R⁶¹² is H or alkyl, R⁶¹³ is H or alkyl, R⁶¹⁴ is H or alkyl, R⁶¹⁵ is H or alkyl, R⁶¹⁶ is H or alkyl, R⁶¹⁷ is H or alkyl, R⁶¹⁸ is H or alkyl, R⁶¹⁹ is H or alkyl, R⁶²⁰ is H or alkyl, R⁶²¹ is H or alkyl, R⁶²² is H or alkyl, R⁶²³ is H or alkyl, R⁶²⁴ is H or alkyl, R⁶²⁵ is H or alkyl, R⁶²⁶ is H or alkyl, R⁶²⁷ is H or alkyl, R⁶²⁸ is H or alkyl, R⁶²⁹ is H or alkyl, R⁶³⁰ is H or alkyl, R⁶³¹ is H or alkyl, R⁶³² is H or alkyl, R⁶³³ is H or alkyl, R⁶³⁴ is H or alkyl, R⁶³⁵ is H or alkyl, R⁶³⁶ is H or alkyl, R⁶³⁷ is H or alkyl, R⁶³⁸ is H or alkyl, R⁶³⁹ is H or alkyl, R⁶⁴⁰ is H or alkyl, R⁶⁴¹ is H or alkyl, R⁶⁴² is H or alkyl, R⁶⁴³ is H or alkyl, R⁶⁴⁴ is H or alkyl, R⁶⁴⁵ is H or alkyl, R⁶⁴⁶ is H or alkyl, R⁶⁴⁷ is H or alkyl, R⁶⁴⁸ is H or alkyl, R⁶⁴⁹ is H or alkyl, R⁶⁵⁰ is H or alkyl, R⁶⁵¹ is

Summary of the invention In one aspect of the invention, novel compounds, pharmaceutical compositions and affective disorders, anxiety, depression Irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immunosuppression, Alzheimer's disease Disease, gastrointestinal tract disorders, anorexia nervosa or other eating disorders, drugs or alcohol Treatment of withdrawal symptoms, drug addiction, inflammatory diseases, fertility problems, etc. induce or promote CRF; achieved or facilitated by antagonizing RF Disorders including, but not limited to, rheumatoid arthritis and deformity Selected from inflammatory disorders such as osteoarthritis, pain, asthma, psoriasis and allergies General anxiety-related disorders, panic, phobia, obsessive-compulsive disorder; post-traumatic stress disorder Harn; stress sleep disorder; pain perception such as fibromyalgia; depression, including major depression, Single seizure depression, recurrent depression, abused child depression, and postpartum depression Mood disorders; dysthymia; bipolar disorders; circulatory temperament, Group; stress headache, cancer, human immunodeficiency virus (HIV) infection; Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's chorea; ulcers Irritable bowel syndrome, Crohn's disease, colon spasm, diarrhea, and psychopathological disorders. Or stress-related postoperative ileus and colon hypersensitivity; anorexia nervosa Are eating disorders such as bulimia nervosa; hemorrhagic stress; stressful psychotic episodes Euthyroid sinus dysfunction syndrome, antidiuretic hormone (ADH) incompatibility syndrome, Obesity, infertility, head trauma; spinal cord trauma; ischemic neuron injury (eg, hippocampus Cerebral ischemia such as ischemia), excitotoxic neuronal damage, epilepsy; hypertension, tachycardia and Cardiovascular and cardiac disorders, including congestive heart failure, stroke, Immune dysfunction, including dysfunction (eg, stress fever, porcine stress syndrome, Cow fever, equine paroxysmal fibrillation, and housekeeping induced dysfunction in chickens Sheep shear stress or dog human-animal interaction stress), muscle Convulsions; urinary incontinence; senile dementia of the Alzheimer type; multi-infarct dementia; amyotrophic lateral sclerosis Chemical dependent or poisoned (eg, alcohol, cocaine, heroin); Drugs, benzodiazepines, or other drugs; drug or alcohol withdrawal symptoms Osteoporosis; for the treatment of sociopsychological dwarfism and hypoglycemia in mammals A method is provided that can be used. The present invention provides a CR by binding to the adrenocorticotrophic hormone releasing factor receptor. Novel compounds that alter the anxiogenic effects of F secretion are provided. Compound of the invention For psychiatric and neurological disorders, anxiety-related disorders, post-traumatic stress disorders Supranuclear palsy and eating disorders and immunological, cardiovascular or heart disease, and For the treatment of colon hypersensitivity associated with psychopathological disorders and stress in mammals Useful In another aspect of the invention, useful as antagonists of corticotropin-releasing factor New compounds of formulas (1) and (2) (described below) are provided. The compounds of the present invention Shows activity as an antagonist of adrenocorticotrophic hormone-releasing factor. Seems to suppress. The present invention comprises the compounds of formulas (1) and (2) Pharmaceutical compositions and suppression of CRF hypersecretion and / or treatment of anxiogenic disorders And a method using the compound. In another aspect of the present invention, compounds provided by the present invention (and especially is a standard for measuring the ability of a potential drug to bind to the CRF receptor It is also useful as a product and a reagent.

Detailed description of the invention (1) The present invention

potential drug to bind to the CAR receptor. It is also useful as a product and a reagent. Detailed description of the invention (1) The present invention relates to an emotional disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic disease, Torres disorder, supranuclear palsy, immunosuppression, Alzheimer's disease, gastrointestinal tract disorders, nervous appetite Poor or other eating disorders, drug addiction, drug or alcohol withdrawal symptoms, inflammatory disorders illness, cardiovascular or heart disease, fertility problems, human immunodeficiency virus (HIV) sensation Stain, hemorrhagic stress, obesity, infertility, head and spinal cord trauma, epilepsy, stroke Ulcers, amyotrophic lateral sclerosis, hypoglycemia, or disorders of CRF CRF-induced or promoted disorder achieved or facilitated by antagonism A method of treating a mammal, such as, but not limited to, a disorder comprising the formula (1)) And compounds of (2), And its isomers, its stereoisomers, or mixtures of its stereoisomers, and drugs A mammal is administered a therapeutically effective amount of a pharmaceutically acceptable salt or prodrug thereof including giving in the above formula. A is N or CR; Z is N or CR¹⁰⁰ And Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, fura Nil, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzof Ranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyran 3,4-dihydro-1,2-benzopyranyl, tetralinyl (each of A is 1-5 R¹⁰⁰ And each Ar is substituted with an unsaturated carbon atom. Joined) R is independently H, C in each case; C_{Four}Alkyl, C_{Two}-C_{Four}Alkenyl, C_{Two}-C_{Four}Alkynyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₇Cycloalkyl Kill, halo, CN, C₁-C_{Four}Selected from haloalkyl, R¹Are independently H, C in each case; C_{Four}Alkyl, C_{Two}-C_{Four}Alkene Le, C_{Two}-C_{Four}Alkynyl, halo, CN, C₁-C_{Four}Haloalkyl, C₁-C₁₂Hid Roxyalkyl, C_{Two}-C₁₂Alkoxyalkyl, C_{Two}-C_{Ten}Cyanoalkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C_{Ten}Cycloalkylalkyl, NR⁶R^{Ten}, C₁-C_{Four}Alkyl-NR⁶R^{Ten}, NR⁶COR^{Ten}, OR¹¹, SH or S (O)_nR¹²Selected from R¹⁰⁰Is H, C₁-C_{Four}Alkyl, C_{Two}-C_{Four}Alkenyl, C_{Two}-C_{Four}Alkynyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C_{Ten}Cycloalkylalkyl, C₁-C_{Four}Hydro Xyalkyl, halo, CN, -NR⁶R⁷, NR⁶COR^{Ten}, -NR⁶(O)_nR⁷, S (O)_nNR⁶R⁷, C₁-C_{Four}Haloalkyl, -OR⁷, SH or -S (O)_nR¹²Selected from R¹⁰⁰Is H, OR⁷, SH, S (O)_nR¹³, COR⁷, CO_{Two}R⁷, OC (O) R¹³, NR⁶COR⁷, N (COR⁷)_{Two}, NR⁶CONR⁶R⁷, NR⁶CO_{Two}R¹³, NR⁶R⁷, NR⁶R^{7a}, N (OR⁷) R⁶, CONR⁶R⁷, Aryl, heteroaryl And heterocyclic groups, Or -C₁-C_{Ten}Alkyl, C_{Two}-C_{Ten}Alkenyl, C_{Two}-C_{Ten}Alkynyl, C_{Three}-C₆Cycloalkyl, C_{Five}-C₈Cycloalkenyl, C_{Four}-C₁₂Cycloalkylalkyl Or C₆-C_{Ten}Cycloalkenylalkyl (each group is independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Halo Alkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{Fifteen}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl and hetero Optionally substituted with 1 to 3 substituents selected from cyclic groups), R¹⁰⁰Is independently in each case C₁-C_{Ten}Alkyl, C_{Two}-C_{Ten}Alkenyl, C_{Two}-C_{Ten}Alkynyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkyl Kill, NO_{Two} Halo, CN, C₁-C_{Four}Haloalkyl, NR⁶R⁷, NR⁶COR⁷, NR⁶CO_{Two}R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO (NOR⁶) R⁷, CO_{Two}R⁷, Or S (O)_nR⁷(C₁-C_{Ten}Alkyl, C_{Two}-C_{Ten}Alkenyl, C_{Two}-C_{Ten}Alkynyl, C_{Three}-C₆Cycloalkyl and C_{Four}-C₁₂Cycloalkylalkyl is independently in each case C₁-C_{Four}Alkyl, NO_{Two} Halo, CN, NR⁶R⁷, NR⁶COR⁷, NR⁶CO_{Two}R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO (NOR⁶) R⁷, Or S (O)_nR⁷ 1-3 pieces selected from which is optionally substituted with a substituent of R⁶And R⁷, R⁶And R^{7a}Are, independently, in each case, -H, -C₁-C_{Ten}Alkyl, C_{Three}-C_{Ten}Alkenyl, C_{Three}-C_{Ten}Alkynyl, haloge C with 1 to 10 atoms; C_{Ten}Haloalkyl, C_{Two}-C₈Alkoxyalkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl, C_{Five}-C_{Ten}Cyclo Alkenyl, or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{Fifteen}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups). Aryl, aryl (C₁-C_{Four}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{Four}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{Four}Alkyl) Selected or Alternatively, NR⁶R⁷And NR⁶R^{7a}Are independently piperidine, pyrrolidine, Perazine, N-methylpiperazine, morpholine or thiomorpholine (each is from 1 to 3 C₁-C_{Four}Optionally substituted with an alkyl group), R⁸Is independently H or C in each case; C_{Four}Selected from alkyl, R⁹And R^{Ten}Are independently H, C in each case; C_{Four}Alkyl, or C_{Three}-C₆Selected from cycloalkyl, R¹¹Is H, C₁-C_{Four}Alkyl, C₁-C_{Four}Haloalkyl or C_{Three}-C₆Cycloa Selected from Luqit, R¹²Is C₁-C_{Four}Alkyl or C₁-C_{Four}Haloalkyl, R¹³Is C₁-C_{Four}Alkyl, C₁-C_{Four}Haloalkyl, C_{Two}-C₆Alkoxyalkyl Le, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl, aryl, Aryl (C₁-C_{Four}Alkyl), heteroaryl, heteroaryl (C₁-C_{Four}Alkyl), R¹⁴Is C₁-C_{Ten}Alkyl, C_{Three}-C_{Ten}Alkenyl, C_{Three}-C_{Ten}Alkynyl, C_{Three}-C₆Cycloalkyl, or C_{Four}-C₁₂Cycloalkylalkyl (each is independently in each case C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, Halo, C₁-C_{Four}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR^{Fifteen}, CO R^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R^{Fifteen}, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{Fifteen}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, And C₁-C₆Alkylthio, C₁-C₆Alkylsulfanyl and C₁-C₆Alkylsulfoni Optionally substituted with 1 to 3 substituents selected from R^{Fifteen}And R¹⁶Are independently H, C in each case; C₆Alkyl, C_{Three}-C_{Ten}Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl (S (O)_nR^{Fifteen}in the case of, R^{Fifteen}Is not H) Aryl is phenyl or naphthyl (each radical in each case Stand up C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo,

<https://patents.google.com/patent/JP2002513382A/en?q=JP2002513382A>

C₁₀Alkyl), heteroaryl, heteroaryl (C₁-C₁₀Alkyl), heterocyclic groups and heterocycles (C₁-C₁₀Alkyl). Neither (9) A is CR, Z is CR^{TWO}, R^{TWO} is H or alkyl, Ar is phenyl, and R^{THREE} is SR¹³ or NR^{6a}R^{7a} in the case of (13) is aryl and heteroaryl R^{6a} and R^{7a} is neither H nor aryl, and is (10) A is CH, Z is CR^{TWO}, R¹ is CR¹¹, R^{TWO} is H, R^{THREE} is OR⁷ and R⁷ and R¹¹ are H, Ar is phenyl, p-Br-phenyl, p-Cl-phenyl, p-NHCOCH₃-phenyl, p-CH₃-phenyl, pyridyl and Neither nor naphthyl. (11) A is CH, Z is CR^{TWO}, R^{TWO} is H, Ar is unsubstituted phenyl, and R^{THREE} is CH₃ or C₁-C₄Alkyl. In the case of F, R¹ is CF₃ and C₁-C₄Alkyl. Nozomi Not so (12) A is CR, R is H, Z is CR^{TWO}, R^{TWO} is OH, and R¹ and R^{THREE} is H Where Ar is not phenyl, (13) A is CR, R is H, Z is CR^{TWO}, R^{TWO} is OH or NH₂, R¹ and R^{THREE} is CH₃ in the case of Ar is 4-phenyl-3-cyano-2-aminopyrido-2-1 is not. [5] The preferred compounds of the invention are compounds of formulas (1) and (2) and isomers, their stereoisomers, or mixtures of stereoisomers, and pharmaceutically acceptable A salt or prodrug thereof, wherein (1) A is N, R¹ is H, C₁-C₁₀Alkyl, halo, CN, C₁-C₁₂Hydroxyalkyl, C₁-C₁₀Alkoxyalkyl or SO₂(C₁-C₁₀Alkyl), R^{THREE} is NR^{6a}R^{7a} in R^{6a} is non Substitution C₁-C₁₀Alkyl in the case of alkyl, R^{7a} is phenyl, naphthyl, thienyl, ben Zothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, Nzothiazolyl, indolyl and C₁-C₁₀Alkyl. None of the cycloalkyls, (2) A is N, R¹ is H, C₁-C₁₀Alkyl, halo, CN, C₁-C₁₂Hydroxyalkyl, C₁-C₁₀Alkoxyalkyl or SO₂(C₁-C₁₀Alkyl), R^{THREE} is NR^{6a}R^{7a} in R^{7a} is unsubstituted C₁-C₁₀Alkyl in the case of alkyl, R^{6a} is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, Benzofuranyl, benzothiazolyl, indolyl and C₁-C₁₀Alkyl. R has the additional condition of not being a kill. [6] In a preferred compound of the invention, Ar is phenyl, pyridyl or 2,3-Dihydrobenzofuranyl (each one to four R^{FOUR} optionally substituted with substituents of the formulas (1) and (2), and isomers thereof, stereoisomers thereof or a mixture of its stereoisomers, and a pharmaceutically acceptable salt or also includes prodrugs. [7] A preferred compound of the invention is that A is N and Z is CR^{TWO}, Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl. Le, R¹ and R^{TWO} is CH₃ and R^{THREE} is NR^{6a}R^{7a} of formulas (1) and (2) and its isomers, its stereoisomers, or mixtures of its stereoisomers, and And pharmaceutically acceptable salts or prodrugs thereof. [11] More preferred compounds of the invention include compounds wherein A is N and isomers thereof, its stereoisomers, or a mixture of its stereoisomers, and pharmaceutically acceptable or a salt or prodrug thereof. [12] The more preferable compound of the invention is a compound, an isomer thereof, and a steric compound thereof. A mixture of isomers, or stereoisomers thereof, and pharmaceutically acceptable salts thereof. Or prodrugs. [13] A more preferred compound of the above invention is a compound wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each having from 1 to 4 R^{FOUR} with substituents optionally substituted compounds and their isomers, their stereoisomers, or their stereoisomers. Mixture of sex forms, including pharmaceutically acceptable salts or prodrugs thereof. [14] A more preferred compound of the above invention is R^{THREE} is NR^{6a}R^{7a} or OR⁷ is A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [15] More preferred compounds of the invention are those wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each having from 1 to 4 R^{FOUR} with substituents optionally substituted, R^{THREE} is NR^{6a}R^{7a} or OR⁷ and a isomer thereof, The stereoisomer, or a mixture of the stereoisomers, and a pharmaceutically acceptable Also includes its salt or prodrug forms. [16] In a more preferred compound of the above invention, Z is CR^{TWO} and the compound isomers, their stereoisomers, or mixtures of stereoisomers, and pharmaceutically acceptable it also includes salts or prodrugs thereof which are acceptable. [17] A more preferred compound of the above invention is a compound wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each having from 1 to 4 R^{FOUR} with substituents Any Substituted compound and its isomer, its stereoisomer, or its stereoisomer And pharmaceutically acceptable salts or prodrugs thereof. [18] A more preferred compound of the invention is a compound represented by the formula: R^{THREE} is NR^{6a}R^{7a} or OR⁷ is A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [19] Further, a more preferred compound of the invention is R^{6a} independently -H, -C₁-C₁₀Alkyl, C₁-C₁₀Alkenyl, C₁-C₁₀Alkynyl, halogen C with 1 to 10 atoms, C₁-C₁₀Alkoxyalkyl, C₁-C₁₀Alkoxyalkyl, C₁-C₁₀Cycloalkyl, C₁-C₁₀Cycloalkylalkyl, C₁-C₁₀Cycloalkenylalkyl, C₁-C₁₀Cycloalkenylalkyl (each group is in each case independently C₁-C₁₀Alkyl, C₁-C₁₀Cycloalkyl, halo, C₁-C₁₀Alkoxyalkyl, cyano, OR^{FIFTEEN}, SH, S (O)_nR¹³, COR^{FIFTEEN}, CO₂R^{FIFTEEN}, OC (O) R¹³, NR⁶COR^{FIFTEEN}, N (COR^{FIFTEEN})₂, NR⁶CONR^{16a}R¹⁵, NR⁶CO₂R¹³, NR^{16a}R^{FIFTEEN}, CONR^{16a}R^{FIFTEEN}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁-C₁₀Alkyl), heteroaryl, heteroaryl Le (C₁-C₁₀Alkyl), a heterocyclic group or a heterocyclic (C₁-C₁₀Alkyl) Selected, R^{7a} are, independently, in each case, -H, -C₁-C₁₀Alkyl, C₁-C₁₀Alkenyl, C₁-C₁₀Alkynyl, halogen C with 1 to 10 atoms, C₁-C₁₀Alkoxyalkyl, C₁-C₁₀Cycloalkyl, C₁-C₁₀Cycloalkylalkyl, C₁-C₁₀Cycloalkenylalkyl, C₁-C₁₀Cycloalkenylalkyl (each group is in each case independently C₁-C₁₀Alkyl, C₁-C₁₀Cycloalkyl, halo, C₁-C₁₀Alkoxyalkyl, cyano, OR^{FIFTEEN}, SH, S (O)_nR¹³, COR^{FIFTEEN}, CO₂R^{FIFTEEN}, OC (O) R¹³, NR⁶COR^{FIFTEEN}, N (COR^{FIFTEEN})₂, NR⁶CONR^{16a}R¹⁵, NR⁶CO₂R¹³, NR^{16a}R^{FIFTEEN}, CONR^{16a}R^{FIFTEEN}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁-C₁₀Alkyl), heteroaryl, heteroaryl Le (C₁-C₁₀Alkyl), a heterocyclic group or a heterocyclic (C₁-C₁₀Alkyl) Selected or Alternatively, NR^{6a}R^{7a} and NR^{6a}R^{7a} is independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine (each The group is 1 to 3 C₁-C₁₀Alkyl (optionally substituted with an alkyl group) A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [20] A more preferred compound of the invention is R^{6a} and R^{7a} are the same, -C₁-C₁₀Alkyl or C₁-C₁₀Cycloalkyl (each group is in this case, independently C₁-C₁₀Alkyl, C₁-C₁₀Cycloalkyl, halo, C₁-C₁₀Alkoxyalkyl, cyano, OR^{FIFTEEN}, SH, S (O)_nR¹³, COR^{FIFTEEN}, CO₂R^{FIFTEEN}, OC (O) R¹³, NR⁶COR^{FIFTEEN}, N (COR^{FIFTEEN})₂, NR⁶CONR^{16a}R¹⁵, NR⁶CO₂R¹³, NR^{16a}R^{FIFTEEN}, CONR^{16a}R^{FIFTEEN}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), and Selected from aryl or heteroaryl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [21] A more preferred compound of the invention is R^{6a} but, -H, -C₁-C₁₀Alkyl, C₁-C₁₀Alkenyl, C₁-C₁₀Alkynyl, halogen C with 1 to 10 atoms, C₁-C₁₀Alkoxyalkyl, C₁-C₁₀Cycloalkyl, C₁-C₁₀Cycloalkylalkyl, C₁-C₁₀Cycloalkenylalkyl, C₁-C₁₀Cycloalkenylalkyl (each group is in each case independently C₁-C₁₀Alkyl, C₁-C₁₀Cycloalkyl, halo, C₁-C₁₀Alkoxyalkyl, cyano, OR^{FIFTEEN}, SH, S (O)_nR¹³, COR^{FIFTEEN}, CO₂R^{FIFTEEN}, OC (O) R¹³, NR⁶COR^{FIFTEEN}, N (COR^{FIFTEEN})₂, NR⁶CONR^{16a}R¹⁵, NR⁶CO₂R¹³, NR^{16a}R^{FIFTEEN}, CONR^{16a}R^{FIFTEEN}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), and Selected from aryl or heteroaryl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [22] A more preferred compound of the invention is R^{6a} and R^{7a} one of them is -C₁-C₁₀Cycloalkyl (each C₁-C₁₀Cycloalkyl is independently in the case of C₁-C₁₀Alkyl, C₁-C₁₀Cycloalkyl, halo, C₁-C₁₀Alkoxyalkyl, cyano, OR^{FIFTEEN}, SH, S (O)_nR¹³, COR^{FIFTEEN}, CO₂R^{FIFTEEN}, OC (O) R¹³, NR⁶COR^{FIFTEEN}, N (COR^{FIFTEEN})₂, NR⁶CONR^{16a}R¹⁵, NR⁶CO₂R¹³, NR^{16a}R^{FIFTEEN}, CONR^{16a}R^{FIFTEEN}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), -Aryl, -heteroaryl or -A heterocyclic group, selected from R^{6a} and R^{7a} is an unsubstituted C₁-C₁₀Alkyl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [23] A more preferred compound of the invention is R^{6a} and R^{7a} is independently H or C₁-C₁₀Alkyl (each C₁-C₁₀Alkyl

The alkyl is in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, Halo, C₁-C_{Four}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Allyl Optionally with 1 to 3 substituents selected from phenyl, heteroaryl and heterocyclic groups. Has been replaced) A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [24] A more preferred compound of the above invention is a compound wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each having from 1 to 4 R^{Four}With substituents Optionally substituted, R^{Three}is NR⁸R^{7a}Or OR⁷And a isomer thereof, The stereoisomer, or a mixture of the stereoisomers, and a pharmaceutically acceptable Also includes its salt or prodrug forms. [25] A more preferred compound of the invention is R^{6a}independently -H, -C₁-C_{Ten}Alkyl, C_{Three}-C_{Ten}Alkenyl, C_{Three}-C_{Ten}Alkynyl, haloge C with 1 to 10 atoms, C_{Ten}Haloalkyl, C_{Two}-C₈Alkoxyalkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl, C_{Five}-C_{Ten}Cyclo Lucenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Five}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁-C_{Four}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{Four}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{Four}Alkyl) Selected, R^{7a}Are, independently, in each case, -H, -C_{Five}-C_{Ten}Alkyl, C_{Three}-C_{Ten}Alkenyl, C_{Three}-C_{Ten}Alkynyl, haloge C with 1 to 10 atoms, C_{Ten}Haloalkyl, C_{Two}-C₈Alkoxyalkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl, C_{Five}-C_{Ten}Cyclo Lucenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Five}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁-C_{Four}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{Four}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{Four}Alkyl) Selected or Alternatively, NR⁶R⁷And NR^{6a}R^{7a}is independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine (each The group is 1 to 3 C₁-C_{Four}Optionally substituted with an alkyl group) A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [26] A more preferred compound of the invention is R^{6a}And R^{7a}Are the same, -C₁-C_{Four}Alkyl or C_{Three}-C₆Cycloalkyl (each group is in this case, independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Five}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups) And -Selected from aryl or heteroaryl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [27] A more preferred compound of the invention is R^{6a}And R^{7a}Are the same, -C₁-C_{Four}Alkyl (each C₁-C_{Four}Alkyl is in each case independent Then C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Haloalkyl, Cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl and heterocyclic groups Arbitrarily substituted with 1 to 3 substituents selected from A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [28] A more preferred compound of the invention is R^{6a}is -H, -C₁-C_{Ten}Alkyl, C_{Three}-C_{Ten}Alkenyl, C_{Three}-C_{Ten}Alkynyl, haloge C with 1 to 10 atoms, C_{Ten}Haloalkyl, C_{Two}-C₈Alkoxyalkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl, C_{Five}-C_{Ten}Cyclo Lucenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Five}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁-C_{Four}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{Four}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{Four}Alkyl) Selected, R^{7a}is -C₁-C_{Four}Alkyl and in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen} 1 to 3 positions selected from, aryl, heteroaryl and heterocyclic groups C optionally substituted with a substituent C_{Four}Is alkyl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [29] A more preferred compound of the invention is R^{6a}And R^{7a}One of them is -C_{Three}-C₆Cycloalkyl (each C_{Three}-C₆Cycloalkyl is independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Low alkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl and multiple Optionally substituted with 1 to 3 substituents selected from cyclic groups), -Aryl, -Heteroaryl or -A heterocyclic group, selected from R^{6a}And R^{7a}is an unsubstituted C₁-C_{Four}Is alkyl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [30] A more preferred compound of the invention is a compound represented by the formula. ^{6a}And R^{7a}is independently H or, C₁-C_{Ten}Alkyl (each C₁-C_{Ten}Alkyl is in each case independent Then C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Haloalkyl, Cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Fifteen}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl and heterocyclic groups Arbitrarily substituted with 1 to 3 substituents selected from A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [31] A more preferred compound of the invention is -Ar is 1 to 4 R^{Four}Phenyl, pyridyl or phenyl optionally substituted with a substituent 2,3-dihydrobenzofuranyl, -R^{Three}is NR^{6a}R^{7a}Or OR⁷And -R¹And R^{Two}Are independently H, C₁-C_{Four}Alkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C_{Ten}, Selected from cycloalkylalkyl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [32] A more preferred compound of the invention is R^{6a}independently -H, -C₁-C_{Ten}Alkyl, C_{Three}-C_{Ten}Alkenyl, C_{Three}-C_{Ten}Alkynyl, haloge C with 1 to 10 atoms, C_{Ten}Haloalkyl, C_{Two}-C₈Alkoxyalkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl, C_{Five}-C_{Ten}Cyclo Lucenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Five}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁-C_{Four}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{Four}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{Four}Alkyl) And R^{7a}is -H, -C_{Five}-C_{Ten}Alkyl, C_{Three}-C_{Ten}Alkenyl, C_{Three}-C_{Ten}Alkynyl, haloge C with 1 to 10 atoms, C_{Ten}Haloalkyl, C_{Two}-C₈Alkoxyalkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C₁₂Cycloalkylalkyl, C_{Five}-C_{Ten}Cyclo Lucenyl or C₆-C₁₄Cycloalkenylalkyl (each group is in each case independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_nR¹³, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁸COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸CONR¹⁶R^{Five}, NR⁸CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups), Aryl, aryl (C₁-C_{Four}Alkyl), heteroaryl, heteroaryl Le (C₁-C_{Four}Alkyl), a heterocyclic group or a heterocyclic (C₁-C_{Four}Alkyl) Selected or Alternatively, NR⁶R⁷And NR^{6a}R^{7a}Are independently piperidine, pyrrolidine, Perazine, N-methylpiperazine, morpholine or thiomorpholine (each Is from 1 to 3 C₁-C_{Four}Optionally substituted with an alkyl group) is there A compound and its isomers, its stereoisomers, or a mixture of its

stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [33] A more preferred compound of the invention is R^{6a} And R^{7a} Are the same, $-C_1-C_{Four}$ Alkyl or $C_{Three}-C_6$ Cycloalkyl (each group is in this case, independently C_1-C_6 Alkyl, $C_{Three}-C_6$ Cycloalkyl, halo, C_1-C_{Four} Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_n R¹³, -COR^{Fifteen}, CO_{Two} R^{Fifteen}, OC (O) R¹³, NR⁸ COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸ CONR¹⁶ R^{1 Five}, NR⁸ CO_{Two} R¹³, NR¹⁶ R^{Fifteen}, CONR¹⁶ R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups) And -Selected from aryl or heteroaryl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [34] A more preferred compound of the invention is R^{6a} And R^{7a} Are the same, $-C_1-C_{Four}$ Alkyl (each C_1-C_{Four} Alkyl is in each case independent Then C_1-C_6 Alkyl, $C_{Three}-C_6$ Cycloalkyl, halo, C_1-C_{Four} Haloalkyl, Cyano, OR^{Fifteen}, SH, S (O)_n R¹³, -COR^{Fifteen}, CO_{Two} R^{Fifteen}, OC (O) R¹³, NR⁸ COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸ CONR¹⁶ R^{Fifteen}, NR⁸ CO_{Two} R^{1 Three}, NR¹⁶ R^{Fifteen}, CONR¹⁶ R^{Fifteen}, Aryl, heteroaryl and heterocyclic groups Arbitrarily substituted with 1 to 3 substituents selected from A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [35] A more preferred compound of the invention is R^{6a} Is -H, $-C_1-C_{Ten}$ Alkyl, $C_{Three}-C_{Ten}$ Alkenyl, $C_{Three}-C_{Ten}$ Alkynyl, halogen C with 1 to 10 atoms, C_{Ten} Haloalkyl, $C_{Two}-C_6$ Alkoxyalkyl, $C_{Three}-C_6$ Cycloalkyl, $C_{Four}-C_{12}$ Cycloalkylalkyl, $C_{Five}-C_{Ten}$ Cyclo Lucenyl or C_6-C_{14} Cycloalkenylalkyl (each group is in each case independently C_1-C_6 Alkyl, $C_{Three}-C_6$ Cycloalkyl, halo, C_1-C_{Four} Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_n R¹³, COR^{Fifteen}, CO_{Two} R^{Fifteen}, OC (O) R¹³, NR⁸ COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸ CONR¹⁶ R^{1 Five}, NR⁸ CO_{Two} R¹³, NR¹⁶ R^{Fifteen}, CONR¹⁶ R^{Fifteen}, Aryl, heteroaryl And optionally substituted with 1 to 3 substituents selected from heterocyclic groups). Aryl, aryl (C_1-C_{Four} Alkyl), heteroaryl, heteroaryl Le (C_1-C_{Four} Alkyl), a heterocyclic group or a heterocyclic (C_1-C_{Four} Alkyl) Selected, R^{7a} Is $-C_1-C_{Four}$ Alkyl and in each case independently C_1-C_6 Alkyl, $C_{Three}-C_6$ Cycloalkyl, halo, C_1-C_{Four} Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_n R¹³, COR^{Fifteen}, CO_{Two} R^{Fifteen}, OC (O) R¹³, NR⁸ COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸ CONR¹⁶ R^{Fifteen}, NR⁸ CO_{Two} R¹³, NR¹⁶ R^{Fifteen}, CONR¹⁶ R^{Fifteen} 1 to 3 positions selected from, aryl, heteroaryl and heterocyclic groups C optionally substituted with a substituent $-C_{Four}$ Is alkyl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [36] A more preferred compound of the invention is R^{6a} And R^{7a} One of them is $-C_{Three}-C_6$ Cycloalkyl (each $C_{Three}-C_6$ Cycloalkyl is independently in the case of $-C_6$ Alkyl, $C_{Three}-C_6$ Cycloalkyl, halo, C_1-C_{Four} Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_n R¹³, COR^{Fifteen}, CO_{Two} R^{Fifteen}, OC (O) R¹³, NR⁸ COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸ CONR¹⁶ R^{Fifteen}, NR⁸ CO_{Two} R¹³, NR¹⁶ R^{Fifteen}, CONR¹⁶ R^{Fifteen}, Aryl, heteroaryl and Optionally substituted with 1 to 3 substituents selected from heterocyclic groups), -Aryl, -Heteroaryl or -A heterocyclic group, selected from R^{6a} And R^{7a} Is an unsubstituted C_1-C_{Four} is alkyl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [37] A more preferred compound of the above invention is R^{6a} And R^{7a} Independently H or C_1-C_{Ten} Alkyl (each C_1-C_{Ten} The alkyl is in each case independently C_1-C_6 Alkyl, $C_{Three}-C_6$ Cyclo Lucil Halo, C_1-C_{Four} Haloalkyl, cyano, OR^{Fifteen}, SH, S (O)_n R¹³, COR^{Fifteen}, CO_{Two} R^{Fifteen}, OC (O) R¹³, NR⁸ COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁸ CONR¹⁶ R^{Fifteen}, NR⁸ CO_{Two} R¹³, NR¹⁶ R^{Fifteen}, CONR¹⁶ R^{Fifteen}, 1-3 selected from aryl, heteroaryl and heterocyclic groups is optionally substituted with a substituent of A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [38] Specific preferred compounds of the invention include compounds of the formula (50) And its isomers, its stereoisomers, or mixtures of its stereoisomers, and drugs A pharmaceutically acceptable salt or prodrug thereof, R^{Threel} Is -NHCH (n-Pr)_{Two}, R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H And R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -N (Et) (n-Bu), R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} But H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -N (n-Pr) (CH_{Two}OPr), R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} But H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (Et) (n-Bu), R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (Et) (CH_{Two}OMe), R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -N (Et)_{Two}, R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (CH_{Two}OMe)_{Two}, R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (CH_{Two}OMe)_{Two}, R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (Et)_{Two}, R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -N (Me) (Ph), R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H Yes R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -N (n-Pr)_{Two}, R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (Et) (n-Pr), R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (CH_{Two}OMe)_{Two}, R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (CH_{Two}OMe)_{Two}, R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} But H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (Et) (CH_{Two}OMe)_{Two}, R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (Et)_{Two}, R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -OEt, R^{4a} Is Cl, R^{4b} Is H, R^{4c} Is Cl, R^{4d} Is H and R^{4e} A compound of formula (50), R^{Threel} Is -N (Et)_{Two}, R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} But H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (Me) (CH_{Two}OMe), R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (Me) (CH_{Two}OMe), R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (Et) (CH_{Two}OMe), R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50) wherein Me is R^{Threel} Is -NHCH (Et)_{Two}, R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} But H and R^{4e} A compound of formula (50) wherein Me is R^{Threel} Is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} But H and R^{4e} A compound of formula (50) wherein Me is R^{Threel} Is -NHCH (CH_{Two}OMe)_{Two}, R^{4a} Is Br, R^{4b} Is H, R^{4c} Is OMe, R^{4d} Is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} Is -NHCH (Et) (CH_{Two}OMe), R^{4a} Is Br, R^{4b} Is H, R^{4c} Is OMe, R^{4d} Is H and R^{4e} A compound of formula (50) wherein Me is R^{Threel} Is -NHCH (CH_{Two}OMe)_{Two}, R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50) wherein Me is R^{Threel} Is -NHCH (CH_{Two}CH_{Two}OMe) (CH_{Two}OMe), R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50) wherein Me is R^{Threel} Is -NHCH (CH_{Two}CH_{Two}OMe) (CH_{Two}OMe), R^{4a} Is Me, R^{4b} Is H, R^{4c} Is Me, R^{4d} Is H and R^{4e} A compound of formula (50), wherein H is R^{Threel} Is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{4a} Is Br, R^{4b} Is H, R^{4c} Is OMe,

R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (Et)_{TWO}, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H Yes R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (Et)_{TWO}, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe)_{TWO}, R^{4a} is CN, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (c-Pr) (CH_{TWO}CH_{TWO}CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe) (CH_{TWO}CH_{TWO}OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (Et)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (Et)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe)_{TWO}, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (CH_{TWO}CH_{TWO}OMe)_{TWO}, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe) (CH_{TWO}CH_{TWO}OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (c-Pr) (CH_{TWO}CH_{TWO}CN), R^{4a} is Me, R^{4b} is H, R^{4c} is O Me, R^{4d} is Me and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (c-Pr) (CH_{TWO}CH_{TWO}CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is (S) -NHCH (CH_{TWO}OMe) (CH_{TWO}CH_{TWO}OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe) (CH_{TWO}CH_{TWO}OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (Et)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (CH_{TWO}CH_{TWO}OMe)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} But H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NH (CH_{TWO}OMe) (CH_{TWO}IPr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (CH_{TWO}CH_{TWO}OMe)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is H, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (CH_{TWO}CH_{TWO}OMe)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_{TWO}, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe) (n-Pr), R^{4a} is Me, R^{4b} is H, R^{4c} But Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OEI) (Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe) (CH_{TWO}CH_{TWO}OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_{TWO}, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (Et)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (Et)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} But H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (Et)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (Et)_{TWO}, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (Et)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_{TWO}, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is (S) -NHCH (CH_{TWO}OMe) (CH_{TWO}CH_{TWO}OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe) (CH_{TWO}CH_{TWO}OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is (S) -NHCH (CH_{TWO}OMe) (CH_{TWO}CH_{TWO}OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OMe) (CH_{TWO}CH_{TWO}OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (c-Pr) (CH_{TWO}CH_{TWO}CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NH (Et) (CH_{TWO}CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (Et)_{TWO}, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (CH_{TWO}CH_{TWO}OMe)_{TWO}, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (CH_{TWO}CH_{TWO}OMe)_{TWO}, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (Et) (CH_{TWO}OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (Et)_{TWO}, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (CH_{TWO}C-Pr) (n-Pr), R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (Et)_{TWO}, R^{4a} is Me, R^{4b} is Me, R^{4c} But OMe, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (Et)_{TWO}, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (Et)_{TWO}, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (CH_{TWO}CH_{TWO}OMe)_{TWO}, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (Et) (CH_{TWO}OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (Et)_{TWO}, R^{4a} is Cl, R^{4b} is H, R^{4c} is CN, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -N (c-Pr) (CH_{TWO}CH_{TWO}CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is O Me, R^{4d} is H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is -NHCH (CH_{TWO}OH)_{TWO}, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} But H and R^{4e} A compound of formula (50) wherein is H R^{Threel} is N (CH_{TWO}CH_{TWO}OMe)_{TWO}, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} But H and R^{4e} is a compound of formula (50) wherein is H. [39] More specifically preferred is 4- (bis- (2-methoxyethyl) amido G) -2,7-dimethyl-8- (2-methyl-4-methoxyphenyl)-[1, 5-a] -Pyrazolo-1,3,5-triazine and isomers thereof, stereoisomers thereof Or a mixture of its stereoisomers, and a pharmaceutically acceptable salt or it is a prodrug. [40] More specifically preferred is 4- (bis- (2-methoxyethyl) amido G) -2,7-dimethyl-8- (2,5-dimethyl-4-methoxyphenyl)- [1,5-a] -Pyrazolo-1,3,5-triazine and its isomers, isomers, or mixtures of stereoisomers thereof, and pharmaceutically acceptable salts thereof Or a prodrug form. [41] More preferred compounds of the above invention are compounds wherein A is CR and the difference thereof. Sex, its stereoisomer, or a mixture of its stereoisomers, and pharmaceutically acceptable Possible salts or prodrugs thereof. [42] More preferred compounds of the invention include compounds, isomers thereof, and steric A mixture of isomers, or stereoisomers thereof, and pharmaceutically acceptable salts thereof. Or prodrugs. [43] A more preferred compound of the above invention is a compound wherein Ar is phenyl, pyridyl or 2, 3-dihydrobenzofuranyl, wherein each Ar is 1 to 4 R^{Four}Place Compound optionally substituted with a substituent and its isomer, its stereoisomer, or its Mixtures of stereoisomers, and pharmaceutically acceptable salts or prodrugs thereof including. [44] A more preferred compound of the above invention is R^{Threel} is NR^{6a}R^{7a}Or OR⁷is A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof. [45] A more preferred compound of the above invention is a compound wherein Ar is phenyl, pyridyl or 2, 3-dihydrobenzofuranyl, wherein each Ar is 1 to 4 R^{Four}Place Optionally substituted with a substituent^{Threel} is NR^{6a}R^{7a}Or OR⁷And the difference Sex, its stereoisomer, or a mixture of its stereoisomers, and pharmaceutically acceptable Also included are the possible salts or prodrugs thereof. [46] In a more preferred compound of the above invention, Z is CR⁷W⁹And the compound Isomers, their stereoisomers, or mixtures of stereoisomers, and pharmaceutically acceptable it also includes salts or prodrugs thereof which are acceptable. [47] A more preferred compound of the above

invention is a compound wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, wherein each Ar is 1 to 4 R^{200f}Place Compound optionally substituted with a substituent and its isomer, its stereoisomer, or its Mixtures of stereoisomers, and pharmaceutically acceptable salts or prodrugs thereof including, [48] A more preferred compound of the above invention is R^{Threel} is NR^{6a}R^{7a}OR⁷ is A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof, [49] More preferred compounds of the above invention are those wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, wherein each Ar is 1 to 4 R^{200f}Place Optionally substituted with a substituent^{Threel} is NR^{6a}R^{7a}OR⁷And the difference Sex, its stereoisomer, or a mixture of its stereoisomers, and pharmaceutically acceptable Possible salts or prodrugs thereof are also included, [50] A more preferred compound of the above invention is R^{6a}And R^{7a}is independently H or, C₁-C_{10n}Alkyl and each C₁-C_{10n}The alkyl is independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{10n}C Low alkyl, cyano, OR^{Fifteen}, SH, S (O)₁₋₁₃, COR^{Fifteen}, CO_{Two}R^{Fifteen}, O C (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{Fifteen}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl and multiple Compounds optionally substituted with 1 to 3 substituents selected from cyclic groups and their compounds isomers, their stereoisomers, or mixtures of stereoisomers, and pharmaceutically acceptable It also includes salts or prodrugs thereof which are acceptable, [51] A more preferred compound of the above invention is -Ar is 1 to 4 R^{200f}Phenyl, pyridyl or phenyl optionally substituted with a substituent 2,3-dihydrobenzofuranyl, -R^{Threel} is NR^{6a}R^{7a}OR⁷and -R⁷And R^{7a}are independently H, C₁-C_{Four}Alkyl, C_{Three}-C₆Cycloalkyl, C_{Four}-C_{Ten}Selected from cycloalkylalkyl A compound and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof, [52] A more preferred compound of the above invention is R^{6a}And R^{7a}is independently H or, C₁-C_{Ten}Alkyl and each C₁-C_{Ten}The alkyl is independently C₁-C₆Alkyl, C_{Three}-C₆Cycloalkyl, halo, C₁-C_{Four}C B Alkyl, cyano, OR^{Fifteen}, SH, S (O)₁₋₁₃, COR^{Fifteen}, CO_{Two}R^{Fifteen}, OC (O) R¹³, NR⁶COR^{Fifteen}, N (COR^{Fifteen})_{Two}, NR⁶CONR¹⁶R^{Fifteen}, NR⁶CO_{Two}R¹³, NR¹⁶R^{Fifteen}, CONR¹⁶R^{Fifteen}, Aryl, heteroaryl and hetero Compounds optionally substituted with 1 to 3 substituents selected from cyclic groups and their differences Sex, its stereoisomer, or a mixture of its stereoisomers, and pharmaceutically acceptable Possible salts or prodrugs thereof are also included, [53] Specific preferred compounds of the invention include compounds of the formula (51)And its isomers, its stereoisomers, or mixtures of its stereoisomers, and drugs A pharmaceutically acceptable salt or prodrug thereof, R^{Threel} is -NHCH (n-Pr)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H And R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (CH_{Two}OMe)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (c-Pr) (CH_{Two}CH_{Two}OMe), R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein H is R^{Threel} is -NHCH (CH_{Two}OMe)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein H is R^{Threel} is -NHCH (Et)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (Et)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein H is R^{Threel} is -N (n-Pr) (CH_{Two}CH_{Two}OMe), R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (n-Bu) (CH_{Two}CH_{Two}OMe), R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (n-Pr) (CH_{Two}OMe), R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (Et)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (Et)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (CH_{Two}OMe)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NH (CH_{Two}CH_{Two}OMe) CH_{Two}OMe, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NH (CH_{Two}CH_{Two}OMe) CH_{Two}OMe, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NH (Et), R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (n-Pr)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (CH_{Two}OMe)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NH (CH_{Two}CH_{Two}OMe) CH_{Two}OMe, R^{6a}is Me, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NH (CH_{Two}CH_{Two}OMe) CH_{Two}OMe, R^{6a}is Me, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (Et)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is (S) -NH (CH_{Two}CH_{Two}OMe) CH_{Two}OMe, R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NH (CH_{Two}CH_{Two}OMe) CH_{Two}OMe, R^{6a}is Cl, R^{6b}is H, R^{6c}is But Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (Et)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (c-Pr) (CH_{Two}CH_{Two}OMe), R^{6a}is Me, R^{6b}is H, R^{6c}is O Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (c-Pr) (CH_{Two}CH_{Two}OMe), R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (n-Pr) (CH_{Two}OMe), R^{6a}is Me, R^{6b}is H, R^{6c}is But OMe, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (n-Pr) (CH_{Two}OMe), R^{6a}is Cl, R^{6b}is H, R^{6c}is But Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (Et)_{Two}, R^{6a}is Br, R^{6b}is H, R^{6c}is OMe, R^{6d}is OMe and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (Et)_{Two}, R^{6a}is Br, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{6a}is Br, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (CH_{Two}OMe)_{Two}, R^{6a}is Br, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (Et)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (Et)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is OMe, R^{6d}is OMe R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (Et)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is OMe, R^{6d}is OMe and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (CH_{Two}CH_{Two}OMe)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Cl, R^{6d}is But H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (CH_{Two}OMe)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (Pr) (CH_{Two}CH_{Two}OMe), R^{6a}is Cl, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -N (8u) (Et), R^{6a}is Cl, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (Et) CH_{Two}OMe, R^{6a}is Cl, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (Et)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (Et)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (Et)_{Two}, R^{6a}is Cl, R^{6b}is H, R^{6c}is Me, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NHCH (Et)_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is Cl, R^{6d}is H and R^{6e}A compound of formula (51) wherein R^{Threel} is -NEt_{Two}, R^{6a}is Me, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}But A compound of formula (51), wherein H is R^{Threel} is -N (Pr) (CH_{Two}CH_{Two}OMe), R^{6a}is Me, R^{6b}is H, R^{6c}is OMe, R^{6d}is H and R^{6e}is a compound of formula (51) wherein H is H: You [54] More specifically preferred is 7-(3-pentylamino)-2,5-di Methyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo Pyrimidine and its isomers, its stereoisomers, or a mixture of its stereoisomers And pharmaceutically acceptable salts or prodrugs thereof, [55] More specifically preferred is 7-(diethylamino)-2,5-dimethyl R-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyri Midine and its isomers, its stereoisomers, or a mixture of its stereoisomers, And pharmaceutically acceptable salts or prodrugs thereof, [56] More specifically preferred is 7-(N-(3-cyanopropyl)-N-Propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-Pyrazolopyrimidine and its isomers, its stereoisomers, or A mixture of its stereoisomers and its pharmaceutically acceptable

salts or prodrugs. Body. The present invention also provides compounds of formulas (1) and (2) and a pharmaceutically acceptable carrier. A pharmaceutical composition comprising the body is provided. Many compounds of the present invention have one or more asymmetric centers or planes. All chiral forms (enantiomers and diastereomers) unless otherwise indicated and racemates are included in the present invention. Many definitions: C = N double bonds, etc. are also present in the compounds of the invention, and all these stable isomers intended during. The compounds of the present invention can be isolated in optically active or racemic forms. It can: Optical activity such as resolution of racemate or synthesis from optically active starting materials. Methods for making sex are well known in the art. Specific stereochemistry or isomer Unless otherwise indicated, all chiral forms (enantiomers and dimers) Asterocmers and racemates, and all geometric isomers are intended.

The term "alkyl" refers to branched and straight-chain alkyls having the specified number of carbon atoms. Includes both IUPAC. Commonly used abbreviations have the following meanings. Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl. The prefix "n" stands for straight-chain alkyl. To taste. The prefix "c" means cycloalkyl. The prefix "(S)" is S The enantiomer, the prefix "(R)" means the R enantiomer. "Alkenyl" is a carbon of either linear or branched structure, such as ethenyl, propenyl, etc. Hydride chain, and one or more that may be at any stable site along the carbon chain. Contains unsaturated carbon-carbon bonds. "Alkynyl" refers to ethynyl, propynyl and the like. Such as a hydrocarbon chain, either straight or branched, and which along the carbon chain it contains one or more carbon-carbon triple bonds that may be at a stable site.

"Halo" "Alkyl" has one or more halogen atoms and has a specified number of carbon atoms. Including both branched and straight chain alkyls. "Alkoxy" is an alkyl of the indicated number of carbon atoms attached through an oxygen bridge. Represents a group. "Cycloalkyl" is cyclopropyl, cyclobutyl, cyclopentyl. Includes monocyclic, bicyclic or polycyclic ring systems, such as ty, cyclohexyl, etc. It is meant to include a saturated cyclic group. "Halo" and "halogen" are fluoro, includes chloro, bromo, and iodo

As used herein, the term "substituted" refers to a single occurrence on a specified atom. Or more than one hydrogen atom is selected and replaced from the indicated group. Provided that the substitution does not exceed the normal valency of the designated atom, it should give stable compounds. When the substitution is keto (i.e., =O), the atom the above two hydrogen atoms are replaced. Combinations of substituents and / or variables are used in combinations where the combination provides stable compounds. Only allowed if "Stable compound" or "stable structure" means that Robust enough to be formulated to an effective therapeutic. Refers to a certain

compound. The term "suitable amino acid protecting group" refers to protecting an amine or carboxylic acid group. Any group known in the related art of organic synthesis is meant. These amines Protecting groups are described in Greene and Wuts, *Protective Groups in Organic Synthesis*, Organic Synthesis, John Wiley & Sons, New York, 1991, and Peptides: Analysis, Synthesis, Biology (The Peptides: Analysis, Synthesis, Biology), Vol. 3, Academic Press, New York, 1981, The disclosure of which is incorporated herein by reference. Any known in the art The amine protecting group of can also be used. Examples of amine protecting groups include: But not limited

to them. 1) Formyl, trifluoroacetyl, Acyl, such as phenyl, phthalyl, and *p*-toluenesulfonyl, Xycarbonyl (Cbz) and substituted benzylloxycarbonyl, 1-(*p*-Biphenyl)-1-methylethoxycarbonyl and 9-fluorenylmethyl Ozyls Aromatic carbamate type such as rubonyl (Fmoc), 3) *t*-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, And aliphatic carbamates such as allyloxycarbonyl, 4) cyclopentene Cyclic alkyls such as isobutyloxycarbonyl and adamantanyloxycarbonyl Carbamate type, 5) allyl type such as trichloromethyl and benzyl, 6) Trialkylsilanes such as trimethylsilane, and 7) phenylthioacids. Forms containing thiols such as nil

The term "pharmaceutically acceptable salts" refers to the compounds of formulas (1) and (2) includes salts with acids or bases. Examples of pharmaceutically acceptable salts include salts such as amines Mineral or organic acid salts of basic residues, alkali salts of acidic residues such as carboxylic acids or the like. Include, but are not limited to, organic salts. Pharmaceutically acceptable salts of the compounds of the present invention are described above in free acid or

base form. Compounds may be combined with stoichiometric amounts of a suitable base or acid, water or organic solvent, or both. By reacting in a mixture of Generally, ether, ethyl acetate (non-aqueous media such as ethanol, isopropanol, or acetonitrile preferable. A list of suitable salts can be found in Remington's Pharmaceutical Sciences, (Pharmaceutical Sciences), 17th edition, Mack Publishing Company, Easton, PA, 1418 1985, the disclosure of which is incorporated herein by reference. A

"prodrug" is used when a prodrug is administered to a mammalian subject, with a covalently bonded carrier that releases the active parent drug of formulas (I) and (II) in vivo. It is believed that there is. Prodrugs of the compounds of formulas (I) and (II) are not. The original compound is cleaved into the original compound, either by routine manipulation or in vivo. Prepared by modifying the functional groups present on the light compounds. Prodrug indicates that a hydroxy, amine, or sulfhydryl group has

been administered to a mammalian subject. Occasional cleavage to free hydroxyl, amino, or sulphydryl groups, respectively. Includes compounds attached to any given group. Examples of prodrugs include compounds of formula (I) Acetate and formic acid of alcohol and amine functions in compounds of formula (II) and (II) including but not limited to esters and benzoate derivatives. Not something. A "therapeutically effective amount" of a compound of the invention is intended to antagonize abnormal levels of CRE. Means an effective amount to treat a symptom such as a host's affective disorder, anxiety or depression. You. **Synthesis**

method. Some compounds of formula (1) were prepared using the method outlined in Scheme 1 to give compounds of formula (7). From the intermediate compound of

Scheme 1 The compound of formula (7) wherein Y is O is not reacted at a reaction temperature in the range of -80 °C to 250 °C. With or without an active solvent, with or without a base, a halo Treatment with a generating agent or a sulfonylating agent gives the product of formula (8) wherein X is halogen, alkanesulfonyloxy, arylsulfonyloxy Xy, or haloalkane-sulfonyloxy). Halogenating agents include SOCl_2 , POCl_3 , PCl_3 , PCl_5 , POBr_3 , PBr_3 , or PBr_5 . But

includes, but is not limited to. Sulfonating agents include alkanes Sulfonic acid halides or anhydrides (methanesulfonyl chloride or Methanesulfonic anhydride, etc.), arylsulfonic acid halides or anhydrides (p-toluenesulfonyl chloride or anhydride) or haloalkyl Sulfonic acid halides or anhydrides (preferably trifluoromethanes Sulfonic acid anhydride). Bases include Alkali metal hydrides (preferably sodium hydride), alkali metal alcohols Oxides (C1-6) (preferably sodium methoxide or sodium Ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (Preferably lithium di-isopropylamide), alkali metal bis (trial) Kirsillyl amides (preferably sodium bis (trimethylsilyl) amide), Trialkylamines (preferably, N, N-di isopropyl N-ethyl Amine or triethylamine) or aromatic amines (preferably pyridine) May be included, but is not limited thereto. Inert solvents include lower alcohols, Lucanitrile (C1-6, preferably acetonitrile), dialkyl Ethers (preferably diethyl ether), cyclic ethers (preferably tetra Hydrofuran or 1,4-dioxane), N, N-dialkylformamides (Preferably dimethylformamide), N, N-dialkylacetamides (preferably Dimethylacetamide), cyclic amides (preferably N-methylpyrrolidic) Zn-2-one), dialkyl sulfioxides (preferably dimethyl sulfoxide), Aromatic hydrocarbons (preferably benzene or toluene) or carbon number Haloalkanes having from 1 to 10 and having 1 to 10 halogen atoms (preferably dichloro Methane) may be included, but not limited to. Preferred reaction temperature Degrees range from -20C to 100C. The compound of formula (8) is treated with an inert solvent at a reaction temperature in the range of -80° C to 250° C. With or without the presence

or absence of a base, a compound of formula $R^{Theo}H$ (where R^{Theo} is as defined above, except that SH , CO_2R^7 , CO_2R^7 , Aryl and A compound of the formula (1) can be produced. Bases include alkali metal hydrides (preferred), Or sodium hydride, alkali metal alkoxides (C1-6) (preferably Me Or sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropyl Ropiramide), alkali metal carbonates, alkali metal bicarbonates, alkali Metal bis (trialkylsilyl) amides (preferably sodium bis (trimethyl Tylsilyl) amide), trialkylamines (preferably N,N -di-iso Propyl-N-ethylamine) or aromatic amines (preferably pyridine) may be included, but not limited to. Inert solvents include alkyl Alcohols (1-8 carbon atoms, preferably methanol or ethanol), low Alkanenitrile (C1-6, preferably acetonitrile), dialkyl Ethers (preferably diethyl ether) and cyclic ethers (preferably Tetrahydrofuran or 1,4-dioxane), N,N -dialkylformamides (preferably dimethylformamide), N,N -dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N -methylpi Rolidine-2-one), dialkyl sulfoxides (preferably dimethyl sulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or charcoal Halocarbones having 1 to 10 halogen atoms and 1 to 10 halogen atoms (preferably Chloromethane), but is not limited thereto. Favorable anti The reaction temperature ranges from $0^\circ C$ to $140^\circ C$. Scheme 2 shows that an intermediate compound of formula (7) where Y is S is prepared by converting some of formula (1) 1 shows an outline of a method for converting into a compound. Scheme 2 The compound of formula (7)

prepared by converting some of formula (1) shows an outline of a method for converting into a compound of formula (2). The compound of formula (2) wherein Y is S is not reacted at a reaction temperature in the range of -80 ° C to 250 ° C. With or without an active solvent and with or without a base, a compound of formula R¹³ X (where R¹³ is as defined above, but aryl and heteroaryl (But not any of the above). Bases include a) Potassium metal hydrides (preferably sodium hydride), alkali metal alkox (C1-C6) (preferably sodium methoxide or sodium ethoxide) Oxides, alkaline earth metal hydrides, alkali metal dialkylamides (preferably Preferably lithium di-isopropylamide), alkali metal carbonates, alkali Metal hydroxides, alkali metal bis (trialkylsilyl) amides (preferably Are sodium bis (trimethylsilyl) amide) and trialkylamines (preferably Gr N, N-diisopropyl-N-ethylamine or triethylamine) Or aromatic amines (preferably pyridine). Set it is not something to be done. As the inert solvent, alkyl alcohols (1-8 carbon atoms, Preferably, methanol or ethanol), lower alkanenitrile (carbon number) 1 to 6, preferably acetonitrile, dialkyl ethers (preferably die Butyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-Dioxane) N-diacylformamides (preferably dimethylformamide), N, N-diacylacetamides (preferably dimethylacetate) Amide), cyclic amides (preferably N-methylpyrrolidin-2-one), dial Kalkauffoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably Benzene or toluene) or a halogen atom having 1 to 10 carbon atoms. Haloalkanes of numbers 1 to 10 (preferably dichloromethane) may be included. It is not limited to

them. Preferred reaction temperatures are in the range of -80 ° C to 100 ° C. It is an enclosure. Formula (12) (R in Formula (1) ^{Three} is SR¹³) The compound of formula (1) It was used to convert a compound of formula (8) as outlined above into a compound of formula (1). Using the same conditions and reagents as in formula R^{Three} Reacting with a compound of formula H to obtain a compound of formula (1) Can be Alternatively, R 12 of formula (12) (R in formula (1) ^{Three} is SR¹³) is reacted with an oxidizing agent in the presence of an inert solvent at a temperature in the range of -80 ° C to 250 ° C. By processing, the expression (15) (R in expression (1)) ^{Three} is S (O)_nR¹³ Where n is 1, 2). Oxidizing agents include hydrogen peroxide, Lucane or aryl peracids (preferably peracetic acid or m-chloro-perbenzoic acid) Acid), dioxirane, oxone or sodium periodate, It is not limited to them. As the inert solvent, alkanones (3 to 10 carbon atoms) are used. , Preferably acetone), water, alkyl alcohols (1-6 carbon atoms), aroma Aromatic hydrocarbons (preferably benzene or toluene) or C1 to C10 Haloalkanes having 1 to 10 halogen atoms (preferably dichloromethane) Or a combination thereof, but is not limited thereto. Oxidizing agent The choice of solvent and solvent is known to those skilled in the art (Uemura, S., 'Sulfur, selenium and others') Oxidation of Sulfur, Selenium and Tellurium " Comprehensive Organic Synthesis, Trost, B.M., (Elmsford, NY: Pergamon Press, 1991), Vol. 7, pp. 762-769). Preferred reaction temperature is -20 ° C-100 ° C. Next, in the formula (13) (R in the formula (1)) ^{Three} is S (O)_nR¹³ And n is 1 or 2), and a compound of formula (8) as outlined in Scheme 1 above) is converted to a compound of formula (1) under the same conditions and reagents as those used in the conversion. Using the formula R^{Three} By reacting with the compound of H, the compound of the formula (1) can be obtained. Formula (1) (where R^{Three} is -NR⁶CDR⁷, -N (CDR⁷)₂, -NR⁶CONR⁶R⁷, -NR⁶CO₂NR¹³, -NR⁶R⁷, -NR⁶SO₂NR⁷ is a compound of From a compound of formula (7), wherein Y is NH, by the method shown in Scheme 3. Can be manufactured. Scheme 3

A compound of the formula (7) (where Y is NH), an alkylating agent and a sulfonylating agent Or a continuous reaction with an acylating agent, or a combination thereof, at -80 ° C to 25 ° C. The reaction should be carried out in an inert solvent with or without a base at a reaction temperature in the range of 0 ° C. By the formula (1) (where R^{Three} is -NR⁶CDR⁷, -N (CDR⁷)₂, -NR⁶CONR⁶R⁷, -NR⁶CO₂NR¹³, -NR⁶R⁷, -NR⁶SO₂NR⁷) Compound can be obtained. Alkylating agents include C₁-C₁₀ Halogenation of alkyl Substances, tosylate, mesylate or triflate; C₁-C₁₀ Haloal Killed (having 1 to 10 halogen atoms) halides, tosylate, mesylate Or triflates; C₁₀-C₆₀ Alkoxyalkyl halides, Toshi Rates, mesylates or triflates; C₃-C₆ Cycloalkyl halo Genides, tosylate, mesylate or triflate; C₁₀-C₁₂ Shi Chloroalkylalkyl halides, tosylate, mesylate or Reflates; aryl (C₁-C₆₀ Alkyl) halides and tosylate, Mesylate or triflate, heteroaryl (C₁-C₆₀ Alkyl) Halides, tosylate, mesylate or triflate, or Prime ring (C₁-C₆₀ Alkyl) halides, tosylate, mesylate and May include, but is not limited to, triflates. Acyl The agent is C₁-C₁₀ Alkanolic acid halides or anhydrides, halogen atoms Number 1 to 10 C₁-C₁₀ Haloalkanoic acid halides or anhydrides, C₁₀-C₆ Alkoxyalkanoic acid halides or anhydrides, C₃-C₆ Cycloalka Acid halides or anhydrides, C₁₀-C₁₂ Halo cycloalkylalkanoates Genides or anhydrides, aromatic carboxylic acid halides or anhydrides, Aryl (C₁-C₆₀ Alkyl) Alkanic acid halides or anhydrides, aromatic heterocycles Carboxylic acid halides or anhydrides, heteroaryl (C₁-C₆₀ Alkyl) Ama Acid halides or anhydrides, heterocyclic carboxylic halides or anhydrides Or heterocycle (C₁-C₆₀ Alkyl) includes alkanolic acid halides or anhydrides But may be, but not limited to. Sulfonylating agents include C₁-C₁₀ Alkyl sulfonic acid halides or anhydrides, having 1 to 10 halogen atoms C₁-C₁₀ Haloalkylsulfonic acid halides or anhydrides, C₁₀-C₆ Alkoxyalkyl sulfonic acid halides or anhydrides, C₃-C₆ Cyclo Alkyl sulfonic acid halides or anhydrides, C₁₀-C₁₂ Cycloalkyl Alkylsulfonic acid halides or anhydrides, arylsulfonic acid halides Or anhydrides, aryl (C₁-C₆₀ Alkyl), heteroaryl Sulfonic acid halides or anhydrides, heteroaryl (C₁-C₆₀ Alkyl) Sulfonic acid halides or anhydrides, heterocyclic sulfonic acid halides, etc. Or anhydrides, or heterocycles (C₁-C₆₀ Alkyl) sulfonic acid halides Or anhydrides, but is not limited thereto. Bases include al Potash gold Hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbon atoms (preferably sodium methoxide or sodium ethoxide), Alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal (Trialkylsilyl) amides (preferably sodium bis (trimethylsilyl) Lyl) amide), trialkylamines (preferably di-isopropylethyl Amines) or aromatic amines (preferably pyridine). It is not limited to these. Inert solvents include alkyl alcohols (carbon Formulas 1 to 8, preferably methanol or ethanol), lower alkanenitrile (C 1-6, preferably acetonitrile), dialkyl ethers (preferably Or diethyl ether), cyclic ethers (preferably tetrahydrofuran or Or 1,4 dioxane), N, N-dialkylformamides (preferably Methylformamide), N, N-dialkylacetamides (preferably dimethyl Luacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one)), Dialkyl sulfoxides (preferably dimethyl sulfoxide) or aromatic Group hydrocarbons (preferably benzene or toluene) may be included, It is not limited to them. Preferred reaction temperatures range from 0 ° C to 100 ° C. . Scheme 4 is based on the formula (7) where Y is O, S, and Z is CR^{Two}(in) 1 shows an outline of a method that can be used for the production of an intermediate compound. Scheme 4. Formula A:CH₂Y₂ The compound of CN is represented by the formula R^{Two}CDR^{Two} (Where R^{Two} is as defined above

And R^{Two} is halogen, cyano, lower alkoxy (C1-6) or lower A compound of alkanoyloxy (having 1 to 6 carbon atoms) and -78 ° C to 200 ° C By reacting in the presence of a base in an inert solvent at a reaction temperature in the range of the formula, The compound of (3) is obtained. Bases include alkali metal hydrides (preferably water Sodium alkoxide), alkali metal alkoxides (C1-6) (preferably Sodium methoxide or sodium ethoxide), alkaline earth metal hydrogenation Substances, alkali metal dialkylamides (preferably lithium di-isopropyl Amides), alkali metal carbonates, alkali metal hydroxides, alkali metal bis (Trialkylsilyl) amides (preferably sodium bis (trimethylsilyl) Amide)), trialkylamines (preferably N, N-di-isopropyl) -N-ethylamine) or aromatic amines (preferably pyridine) Good, but not limited to them. Inactive solvents include alkyl alcohol (C1-8, preferably methanol or ethanol), lower alk Nitriles (C1-6, preferably acetonitrile), water, dialkyl Ethers (preferably diethyl ether), cyclic ethers (preferably tetra Hydrofuran or 1,4-dioxane), N, N-dialkylformamides (Preferably dimethylformamide), N, N-dialkylacetamides (preferably Or dimethylacetamide), cyclic amides (preferably N-methylpyrrolidone 2-one), dialkyl sulfoxides (preferably dimethyl sulfoxide)) Or aromatic hydrocarbons (preferably benzene or toluene) Good, but not limited to them. Preferred reaction temperature is 0 ° C to 100 ° C Range. The compound of formula (3) is prepared at a temperature in the range of 0 ° C to 200 ° C, preferably 70 ° C to 15 ° C. By reacting with hydrazine hydrate in the presence of an inert solvent at a temperature of 0 ° C. And the compound of formula (4) is obtained. Inactive solvents include water, alkyl alcohols (C1-C8, preferably methanol or ethanol), lower alkanenit Ryls (C1-6, preferably acetonitrile), cyclic ethers (preferably Or tetrahydrofuran or 1,4 dioxane), N, N-dialkylform Muamides (preferably dimethylformamide), N, N-dialkylacetacetates Amides (preferably dimethylacetamide) and cyclic amides (preferably N-meth Tylpyrrolidin-2-one), dialkyl sulfoxides (preferably dimethyl Sulfoxide) or aromatic hydrocarbons (preferably benzene or toluene) May be included, but is not limited thereto. A compound of formula (4) The presence of an inert solvent, the presence of an acid, or the presence of an acid at a temperature ranging from 0 ° C to 200 ° C. Without the formula (5) (where R⁶ is a compound having 1 to 6 carbon atoms) Thereby, the compound of the formula (6) can be produced. Acids have 2 to 2 carbon atoms 10 alkanolic acids (preferably acetic acid) having 2 to 10 carbon atoms and 1 halogen atom Haloalkanoic acid such as trifluoroacetic acid, arylsulfonic acid (preferably K is p -Toluenesulfonic acid or benzenesulfonic acid), an alkane having 1 to 10 carbon atoms Contains sulfonic acid (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid, But is not limited thereto. Uses stoichiometric or catalytic amounts of acid Can be. Examples of the inert solvent include water and alkanenitrile (C 1-6, Preferably acetonitrile), a halo having 1 to 6 carbon atoms and 1 to 6 halogen atoms. Lucanes (preferably dichloromethane or chloroform), having 1 to 10 carbon atoms Alkyl alcohols (preferably ethanol) and dialkyl ethers (charcoal A prime number of 4 to 12, preferably diethyl ether or di-isopropyl ether) Or cyclic ethers such as dioxane or tetrahydrofuran. However, it is not limited to them. Preferred temperatures are between ambient temperature and 100 ° C. Range A compound of formula (6) is reacted in an inert solvent at a reaction temperature ranging from -50 ° C to 200 ° C, The formula Y = C (R⁶)₂ (Where Y is O or S R⁶ is halogen (preferably chlorine), alkoxy (1-4 carbon atoms) or By treating with a compound of the formula (7) Can be converted to the compound of Bases include alkali metal hydrides (preferably hydrogenated Sodium), alkali metal alkoxides (C1-6) (preferably nato Lium methoxide or sodium ethoxide), alkali metal carbonates, Potassium metal hydroxides, trialkylamines (preferably N, N-di-isoprop Propyl-N-ethylamine or triethylamine) or aromatic amines (preferably Preferably pyridine), but is not limited thereto. Inactivity Examples of the aprotic solvent include alkyl alcohols (1-6 carbon atoms, preferably methanol and the like), Or ethanol), lower alkanenitrile (having 1 to 6 carbon atoms, preferably Nitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-d Oxane), N, N-dialkylformamides (preferably dimethylforma Amide), N, N-dialkylacetamides (preferably dimethylacetamide), Cyclic amides (preferably N-methylpyrrolidin-2-one), dialkyl Sulfoxides (preferably dimethyl sulfoxide) or aromatic hydrocarbons (Preferably, but not limited to, benzene or toluene), thing is not. Preferred temperatures are between 80 and 150°C. The intermediate compound of formula (7) (where Z is N) is prepared according to the scheme outlined in Scheme 5. It can be synthesized according to

the method.

Scheme 5 Formula $ArCH_2R^{Two}$ The compound of CN is represented by the formula $R^1CH_2R^{Two}N^{Three}$ (Where R^1 is H, alkyl (Phenyl optionally substituted with C1-5) or alkoxy (C1-6) And a base in an inert solvent at a temperature in the range of 0 ° C to 200 ° C. In Reaction with or without the formation of the compound of formula (9). Can be. Bases include alkali metal hydrides (preferably sodium hydride), Alkali metal alkoxides (C1-6) (preferably sodium methoxide) Sid, sodium ethoxide or potassium t-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis (trialkylsilyl) amides (preferably sodium bis (trimethyl Tilsilyl) amide), trialkylamines (preferably N, N-di-isopropyl-N-ethylamine or triethylamine) or aromatic amines (preferably pyridine), but is not limited thereto. Unfortunate As the active solvent, alkyl alcohols (1-8 carbon atoms, preferably methanol Or ethanol), lower alkanenitrile (having 1 to 6 carbon atoms, preferably Tontitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers Ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-Dialkylformamides (preferably dimethylformamide), N, N-di Alkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkyl sulfoxides (preferably Dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene Or toluene), but is not limited thereto. Like New reaction temperatures range from ambient to 100 ° C. Treating the compound of formula (9) with a reducing agent in an inert solvent at -100 ° C to 100 ° C thereby, the compound of the formula (10) is obtained. The reducing agent includes (a) Pd-carbon, PtO_{Two} Noble metal catalysts such as, Pt-carbon, Rh-alumina or Raney nickel (b) liquid ammonia and alkali metals (preferably Or (c) ceric ammonium nitrate. It is not limited to them. Inactive solvents include alkyl alcohols (carbon number 1 to 8, preferably methanol or ethanol), lower alkanenitrile (C1-6, preferably acetonitrile), water, dialkyl ethers (preferably Or diethyl ether), cyclic ethers (preferably tetrahydrofuran or Was Is 1,4-dioxane), N, N-dialkylformamides (preferably Tyiformamide), N, N-dialkylacetamides (preferably dimethyl Acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), Dialkyl sulfoxides (preferably dimethyl sulfoxide) or aromatic Hydrocarbons (preferably benzene or toluene) may be included However, the present invention is not limited to this. Preferred reaction temperatures are between -500 and 600. Next Wherein the compound of formula (9) is obtained by converting formula (4) to formula (7) (where Z is CR^{Two}) Using the reagents and reaction conditions outlined in Scheme 4 when converting to The compound of formula (7) (where Z is N) is converted via the intermediate of (11). It is. The compound of formula (1) is prepared by reacting the compound of formula (7) (where Y is O, S and Z is as defined above).

Scheme 6 Dehydration of the compound of formula (7) in an inert solvent at a reaction temperature in the range of 0 ° C to 250 ° C. In the presence of an agent, the formula $R^{Three}H$ compound. Dehydrating agents include $P_{Two}O_{Five}$, Molecular sieves or inorganic or organic acids It is not limited. Acids include alkanic acids having 2 to 10 carbon atoms (preferably vinegar), Acid, arylsulfonic acid (preferably p-toluenesulfonic acid or benzene Sulfonic acid), an alkanesulfonic acid having 1 to 10 carbon atoms (preferably methanesulfonic acid) Acid, hydrochloric acid, sulfuric acid or phosphoric acid, but is not limited thereto. There is no. As the inert solvent, alkyl alcohols (1 to 8 carbon atoms, preferably Methanol or ethanol), lower alkanenitrile (C1-6, preferably Or a Cetonitrile), dialkyl ethers (preferably glyme or diglyme), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylformamides (preferably dimethylformamide), N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkyl sulfoxide (preferably dimethyl sulfoxide), aromatic hydrocarbons (preferably benzene) Halo having 1 to 10 carbon atoms and 1 to 10 halogen atoms. Loalkanes (preferably chloroform) may be included, but are not limited thereto. Not something. Preferred reaction temperatures range from ambient to 150 ° C. Some compounds of Formula (1), wherein A is N, are also shown in Scheme 7. It can be manufactured by the following method.

Scheme 7 An intermediate compound of formula (14), wherein Z is as defined above, is treated at 0 ° C. In an inert solvent at a temperature in the range of 2 5 0 250 ° C, with or without the presence of an acid, the formula $R^{Three}C(OR^{Two})$ (Where R^1 is a compound of alkyl (C1-6) Can be done. The acid includes an alkanic acid having 2 to 10 carbon atoms (preferably acetic acid), Aryl sulfonic acid (preferably p-toluene sulfonic acid or benzene sulfo Acid), alkanesulfonic acid having 1 to 10 carbon atoms (preferably methanesulfonic acid), Hydrochloric acid, sulfuric acid or phosphoric acid, but is not limited to. Stoichiometric or catalytic amounts of these acids can be used. Inert solvents, Lower alkanenitrile (C1-6, preferably acetonitrile), dia Le Kil ethers (preferably diethyl ether), cyclic ethers (preferably Tetrahydrofuran or 1,4-dioxane), N, N-dialkylforma Amides (preferably dimethylformamide), N, N-dialkylacetamide (preferably dimethylacetamide), cyclic amides (preferably N-methyl Pyrrolidin-2-one), dialkyl sulfoxides (preferably dimethyl sulfone) Foxide), aromatic hydrocarbons (preferably benzene or toluene) or Haloalkanes having 1 to 10 carbon atoms and 1 to 10 halogen atoms (preferably di Chloromethane), but is not limited thereto. preferable Reaction temperatures range from 500 to 1500. The intermediate compound of formula (7) can also be synthesized by the reaction shown in Scheme 8.

Scheme 8 Formula (15) (where Y is OH, SH, NR^2 And Z is the communication defined above. X is Br, Cl, I, $O_{Three}SCF_{Three}$ Or B (OR^{Two})_{Two} And R^{Two} is H or an alkyl (1-6 carbon atoms) compound at -100 ° C to 200 ° C. The presence or absence of a base in an inert solvent at a temperature in the range of Formulas ArM, with or without the presence of a medium, wherein M is a halogen, an alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl_{Two}, Ce Br_{Two} Or copper halides). Business As will be appreciated by those skilled in the art, the reagent ArM can be formed during the reaction. Organic metal touch Medium is a palladium phosphine complex (Pd (PPh_{Three})_{Four} Etc.), halogenated palladium Or palladium alkanoate (PdCl_{Two}(PPh_{Three})_{Two} Or Pd (OAc)_{Two} Or nickel complexes (NiCl_{Two}(PPh_{Three})_{Two} Etc.) But not limited to them. Bases include alkali metal carbonates and Is a trialkylamine (preferably N, N-di-isopropyl-N-ethyl) Amine or triethylamine), but is not limited thereto. There is no. As the inert solvent, 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), dialkyl sulfoxides (preferably dimethyl sulfoxide), aromatic hydrocarbons (preferably Benzene or toluene) or water, including but not limited to is not. Preferred reaction temperatures range from -500 to 1000. The choice of M and X is known to those skilled in the art (Imamoto, T., "Organic Selenium", Organocerium Reagents", Comprehensive Organic Synthesis Synthesis), Trost, B.M., (Elmsford, NY: Pergamon Press, 1991), 1 Vol. 231-250, Knoche, P., "Organic Zinc, Organic Cadmium, and Organic Mercury Reagents (Organozinc, Organocadmium, and Organomercury Reagents)", Comprehensive Organic Synthesis, Trost, B.M., (Elmsford, NY: Pergamon Press, 1991), 1 Volume, pp. 211-230, Knight, D.W., "sp^{Two} Coupling reaction between carbon centers (Coupling Reactions between sp^{Two} Carbon Centers), Comprehensive Organic Synthesis, Trost, B.M., Ed., (Elmsford, NY: Pergamon Press, 1991), Volume 3, pages 481-520). Compounds of formula (1) can also be prepared using the method shown in Scheme 9.

Scheme 9 Formula (16) (where A, Z, R^{Two} And R^{Three} is as defined above, and X is Br, Cl, I, $O_{Three}SCF_{Three}$ Or B (OR^{Two})_{Two} Where R^{Two} is H or carbon At a temperature ranging from -100 ° C to 200 ° C. In an inert solvent, in the presence or absence of a base, and in the presence of an organometallic catalyst, Or without the formula ArM (where M is halogen, alkali metal, ZnCl, Zn Br, ZnI, MgBr, MgCl, MgI, CeCl_{Two}, CeBr_{Two} Or halo (Generative copper compounds). As those skilled in the art will appreciate The reagent ArM can be generated during the reaction (Previous in "Comprehensive Organic Synthesis" References). Organometallic catalysts include palladium phosphine complexes (Pd (PPh_{Three})_{Four}), Palladium halides or palladium alkanoate salts (PdCl_{Two}(PPh_{Three})_{Two} Or Pd (OAc)_{Two} Or nickel complexes (NiCl_{Two}(PPh_{Three})_{Two} Etc.), but is not limited thereto. Bases include alkali metal carbonates or trialkylamines (preferably N, N-di-isopropyl-N-ethylamine or triethylamine). But is not limited thereto. Inactive solvents include dialkyl ethers, Ters (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylformamides (Dimethylformamide), N, N-dialkylacetamides (preferably Dimethylacetamide), thioamide amides (preferably N-methylpyrrolidin-2-one), dialkyl sulfoxides (preferably dimethyl sulfoxide), Aromatic hydrocarbons (preferably benzene or toluene) or water Be Good, but not limited to them. The preferred reaction temperature is -500 to 100. It is in the range of 0 ° C. Formula (7) (where Y is O, S, NH, and Z is CR^{Two} And R^{Two}, R^{Three} And R^{Two} is as defined above), wherein the intermediate compound is illustrated in Scheme 10. Thus, it can be manufactured.

Scheme 10 A compound of the formula (3) is converted into a base or an acid in an inert solvent at a temperature of 0 ° C to 250 ° C. H, with or without presence $TwoNH$ (C = Y) NH_{Two} (Where Y is O, S or NH) to form a compound of formula (17) be able to. Acids include alkanic acids having 2 to 10 carbon atoms (preferably acetic acid), Sulfonic acid (preferably p-toluenesulfonic acid or benzenesulfonic acid), C 1-10 alkanesulfonic acid (preferably methanesulfonic acid), salt An acid, sulfuric acid or phosphoric acid may be included, but is not limited to. Conversion Stoichiometric or catalytic amounts of these acids can be used. Bases include alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (charcoal Prime 1-6) (preferably sodium methoxide or sodium ethoxide), Alkaline earth metal hydrides, alkali metal dialkylamides (preferably Lithium di-isopropylamide), alkali metal bis (trialkylsilyl) Amides (preferably sodium bis (trimethylsilyl) amide), trialkylamines (preferably N, N-di-isopropyl-N-ethylamine or Contains triethylamine) or aromatic amines (preferably pyridine) Good, but not limited to them. Inactive solvents include alkyl alcohol (C 1-6), lower alkanenitrile (C 1-6), dialkyl ethers (preferably diethyl ether), cyclic ethers Ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-Dialkylformamides (preferably dimethylformamide), N, N-di Alkylacetamides (preferably

dimethylacetamide), cyclic amides (preferably, N-methylpyrrolidin-2-one), dialkyl sulfoxides (preferably dimethyl sulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or a haloalkane having 1 to 10 carbon atoms and 1 to 10 halogen atoms. Gaseous (preferably dichloromethane) may be included, but are not limited thereto. Not. Preferred reaction temperatures range from 0 ° C to 150 ° C. Then, the compound of formula (17) The product in the presence or presence of an acid in an inert solvent at a temperature ranging from 0 ° C to 250 ° C. Without, R^{Three} is a compound of alkyl (C1-6) Can respond. Acids include alkanic acids having 2 to 10 carbon atoms (preferably acetic acid), Arylsulfonic acid (preferably p-toluenesulfonic acid or benzenesulfonic acid) Sulfonic acid having 1 to 10 carbon atoms (preferably methanesulfonic acid), Hydrochloric acid, sulfuric acid or phosphoric acid, but is not limited thereto. No. Stoichiometric or catalytic amounts of these acids can be used. Inert solvent: Are lower alkane nitriles (1-6 carbon atoms, preferably acetonitrile), di Alkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylform Moore Amides (preferably dimethylformamide), N, N-dialkylacetamide (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkyl sulfoxides (preferably dimethyl sulfoxide) Foxide, aromatic hydrocarbons (preferably benzene or toluene) or Haloalkanes having 1 to 10 carbon atoms and 1 to 10 halogen atoms (preferably di Chloromethane), but is not limited thereto. preferable Reaction temperatures range from 50C to 150C. Scheme 11 includes formula (1) (wherein R^{Three} is COR², CO₂WR², NR³COR² And CONR⁶R² At a temperature in the range of -80 ° C to 250 ° C. Treatment with a reducing agent in an active solvent, with or without the presence of an acid, yields a compound of formula (1) R^{Three} is CH (OH) R², CH₂WR²OH, NR³CH₂WR² And

CH₂WR⁶NR³ is B) shows methods that can be used to convert other compounds.

Scheme 11 Reducing agents include alkali metal or alkaline earth

metal boron hydrides (preferably Or lithium or sodium borohydride), borane, dialkylboranes (Di Isomylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkyl) aluminum hydrides or dialkylaluminum hydrides (diisobutyl hydride Aluminum, etc.), but is not limited thereto. Inert solution Examples of the medium include alkyl alcohols (C1-6) and dialkyl ethers (preferred), i Or diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene), but is not limited thereto. Preferred reaction temperature is in the range of -80C to 100C. Scheme 12 includes the formula (1) (wherein R^{Three} is COR² Or CO₂WR² is) The compound is reacted with a compound of formula R in an inert solvent at a temperature ranging from -80 ° C to 250 ° C. /M reagents And then processing formula (1) (where R^{Three} is C (OH) (R²)_{Two} To another compound Here are some methods that can be used to convert.

Scheme 12 M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, Mg Cl, MgI, CeCl₂WR², CeBr₂WR² Or copper halides. Inert solvent include dialkyl ethers (preferably diethyl ether) and cyclic ethers (preferably tetrahydrofuran) or aromatic hydrocarbons (preferably Benzene or toluene), but is not limited thereto. Good Preferred reaction temperatures are in the range of -80C to 100C. Formula (1) (where R^{Three} is -NR³COR², N (COR²)_{Two}, -NR³CONR⁶ R², -NR³CO₂WR², -NR³R², -NR³SC₂WR² is a compound of it can be synthesized as shown in Scheme 13.

Scheme 13 Formula (18) (wherein R and R¹ is as defined above), The

presence or presence of the base in an inert solvent at a temperature in the range of -50 ° C to 250 ° C. Without further reaction with a compound of formula (4) or (10) to form a compound of formula (19). Can be made. Bases include alkali metal hydrides (preferably hydrogenated sodium Re), Alkali metal alkoxides (C1-6) (preferably sodium) Methoxide or sodium ethoxide, alkaline earth metal hydrides, Potassium metal dialkylamides (preferably lithium di-isopropylamide), Alkali metal carbonates, alkali metal bis (trialkylsilyl) amides (preferably sodium bis (trimethylsilyl) amide), trialkylamines (preferably diisopropylethylamine) or aromatic amines (preferably Or pyridine) may be included, but is not limited thereto. Inert solution As the medium, alkyl alcohols (1 to 8 carbon atoms, preferably methanol or Ethanol), lower alkane nitriles (C 1-6, preferably acetonitrile Lyl), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dia Alkylformamides (preferably dimethylformamide), N, N-dialkyl Ruacetamides (preferably dimethylacetamide), cyclic amides (preferably Or N-methylpyrrolidin-2-one), dialkyl sulfoxides (preferably Is dimethyl sulfoxide) or aromatic hydrocarbons (preferably benzene or May include, but is not limited to, toluene. Favorable anti: The reaction temperature ranges from 0 ° C to 100 ° C. Then, a compound of the formula (19) and an alkylating agent, sulfonylating agent or acyl The continuous reaction with the agent, or a combination thereof, is carried out in the range of -80 ° C to 250 ° C. By carrying out in an inert solvent with or without a base at the reaction temperature, Formula (1) (wherein R^{Three} is -NR³COR², N (COR²)_{Two}, -NR³CONR⁶ R², -NR³CO₂WR², -NR³R², -NR³SC₂WR² is obtained) Can be Alkylating agents include C₁-C_{Ten}Alkyl halides; Silates, mesylates or triflates; C₁-C_{Ten}Haloalkyl (Ha Halides, tosylate, mesylate having 1 to 10 logogen atoms or Triflates; C_{Two}-C₉Alkoxyalkyl halides and tosylate, Mesylate or triflate; C₁H_{See}-C₆Cycloalkyl halides, Tosylate, mesylate or triflate; C_{Four}-C₁₂Cycloalkyl Halides, tosylate, mesylate or triflate; C₁-C_{Four}Alkyl halides, tosylate, mesylate Or triflates; heteroaryl (C₁-C_{Four}Alkyl) halides, Tosylate, mesylate or triflate; or heterocyclic (C₁-C_{Four} Alkyl) halides, tosylate, mesylate or triflate Classes may be included, but are not limited thereto. The acylating agent includes C₁-C_{Ten}Alkanic acid halides or anhydrides, C 1-10 halogen atoms₁-C_{Ten}Haloalkanoic acid halides or anhydrides, C_{Two}-C₉Alkoxy Lucanoic acid halides or anhydrides, C_{Three}-C₆Cycloalkanoic acid halogenation Or anhydrides, C_{Four}-C₁₂Cycloalkylalkanoic acid halides or Are anhydrides, aromatic carboxylic acid halides or anhydrides, aryl (C₁-C_{Four}) Alkanic acid halides or anhydrides, aromatic heterocyclic carboxylic acids Logenides or anhydrides, heteroaryl (C₁-C_{Four}) Halogen alkanate Or anhydrides, heterocyclic carboxylic halides or anhydrides, or Prime ring (C₁-C_{Four}) Alkanic acid halides or anhydrides. It is not limited to them. Sulfonylating agents include C₁-C_{Ten}Alkyls Sulfonic acid halides or anhydrides, C 1-10 halogen atoms₁-C_{Ten}Haloalkylsulfonic acid halides or anhydrides, C_{Two}-C₉Alkoxy Alkyl sulfonic acid halides or anhydrides, C_{Three}-C₆Cycloalkylsul Phonic acid halides or anhydrides, C_{Four}-C₁₂Cycloalkylalkylsul Halonic acid halides or anhydrides, aromatic sulfonic acid halides or Anhydrides, aryl (C₁-C_{Four}Alkyl), heteroarylsulfonic acid halide Or anhydrides, heteroaryl (C₁-C_{Four}Alkyl) sulfonic acid halo Genides or anhydrides, heterocyclic sulfonic acid halides or anhydrides, Or a heterocyclic ring (C₁-C_{Four}Alkyl) sulfonic acid halides or anhydrides Includes, but is not limited to. Bases include alkali metal hydrogenation (preferably sodium hydride), alkali metal alkoxides (C 1 ~ 6) (preferably sodium methoxide or sodium ethoxide), Potassium earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis (tri- Alkyl sil L) amides (preferably sodium bis (trimethylsilyl) amide) Alkylamines (preferably di-isopropylethylamine) or aromatic Amines (preferably pyridine) may be included, but are not limited thereto. There is no. As the inert solvent, alkyl alcohols (1 to 8 carbon atoms, preferably Methanol or ethanol), lower alkane nitriles (C1-6, preferably Or acetonitrile), dialkyl ether (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylformamides (preferably Or dimethylformamide), N, N-dialkylacetamides (preferably Is dimethylacetamide), cyclic amides (preferably N-methylpyrrolidine- 2-one), dialkylsulfox (preferably dimethyl sulfoxide) or aromatic hydrocarbon (preferably, Benzene or toluene), but is not limited thereto. No. Preferred reaction temperatures range from 0 ° C to 100 ° C. Compounds of the formula (1) wherein A is CR and R is as defined above Can be synthesized by the method shown in Scheme 14.

Scheme 14 Compounds of formula (4) or (10) are inertly dissolved at a temperature in the range in the medium, the compound of formula (20) (wherein R¹ And R^{Three} is above By treatment with a compound of the formula (1) wherein A is CR and R is as defined above). Base, Alkali metal hydrides (preferably sodium hydride), alkali metal Ko Oxides (C1-6) (preferably sodium methoxide or sodium Ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, Potassium metal bis (trialkylsilyl) amides (preferably sodium bis (Trimethylsilyl) amide), trialkylamines (preferably di-isopro Pyrethylamine) or aromatic amines (preferably pyridine). However, it is not limited to them. Inactive solvents include alkyl alcohol (1-8 carbon atoms, preferably methanol or ethanol), lower alkane nitriles (C1-6, preferably acetonitrile), dialkyl ether (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-dialkylformamides (preferably Or dimethylformamide), N, N-dialkylacetamides (preferably Is dimethylacetamide), cyclic amides (preferably N-methylpyrrolidine- 2-one), dialkyl sulfoxides (preferably dimethyl sulfoxide) and the like. Or aromatic hydrocarbons (preferably benzene or toluene) However, it is not limited to them. Preferred reaction temperatures are in the range of 0 ° C to 100 ° C. It is an enclosure. Alternatively, a compound of formula (1) wherein A is CR and R is as defined above is synthesized via intermediates of formulas (22) and (23) Can be Dissolving the compound of formula (4) or (10) in an inert solution at a temperature ranging from 0 ° C to 250 ° C; In the medium, the compound of the formula (21) (wherein R¹ is defined above And R⁴ is to treat with alkyl (C1-6) compound Of formula (1) (where A is CR and R is as defined above) A compound can be obtained. Bases include alkali metal hydrides (preferably water Sodium alkoxide), alkali metal alkoxides (C1-6) (preferably Sodium methoxide or sodium ethoxide), alkaline earth metal hydrogenation Substances, alkali metal dialkylamides (preferably lithium di-isopropyl Amide), alkali metal

carbonates, alkali metal bis (trialkylsilyl) Amides (preferably sodium bis (trimethylsilyl) amide), trialkyl Lure Amines (preferably di-isopropylethylamine) or aromatic amines (preferably pyridine), but is not limited thereto. Inactivity Examples of the aprotic solvent include alkyl alcohols (1-8 carbon atoms, preferably methanol and the like), Or ethanol), lower alkanenitrile (having 1 to 6 carbon atoms, preferably Nitriles), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N, N-Dialkylformamides (preferably dimethylformamide), N, N-Dia Alkylacetamides (preferably dimethylacetamide) and cyclic amides (preferably N-methylpyrrolidin-2-one) and dialkyl sulfoxides (preferably dimethyl sulfoxide) or aromatic hydrocarbons (preferably benzene Or toluene) may be included, but is not limited thereto. Preferred Reaction temperatures range from 0 ° C to 150 ° C. The compound of formula (22) is treated at -80 ° C Base present with or without inert solvent at reaction temperatures in the range of 250 ° C By treating with or without a halogenating or sulfonylating agent, Formula (23) (wherein X is halogen, alkanesulfonyloxy, arylsulfur Phonyloxy or haloalkanesulfonyloxy) Can be. Halogenating agents include SOCl_2 , POCl_3 , PCl_3 , PCl_5 , PCl_6 , PO Br_3 , PBr_3 Or PBr_5 . Including, but not limited to. Sulfonylating agents include alkanesulfonic acid halides or anhydrides (methanesulfonyl chloride or methanesulfonic anhydride), arylsulfur Phonic acid halides or anhydrides (p-toluenesulfonyl chloride or Is an anhydride or the like) or a haloalkylsulfonic acid halide or an anhydride (Trifluoromethanesulfonic anhydride), but is not limited thereto. It is not something to be done. Bases include alkali metal hydrides (preferably hydrogenated Thorium), alkali metal alkoxides (C1-6) (preferably sodium Methoxide or sodium ethoxide), alkaline earth metal hydrides, Alkali metal dialkylamides (preferably lithium di-isopropylamide), Alkali metal bis (trialkylsilyl) amides (preferably sodium Bis (trimethylsilyl) amide), trialkylamines (preferably N, N-Di-isopropyl-N-ethylamine or triethylamine) or aromatic alcohol Mines (preferably pyridine) may be included, but are not limited thereto. Absent. The inert solvent includes lower alkanenitrile (having 1 to 6 carbon atoms, preferably (Cetonitrile), 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), dialkyl sulfoxides (Preferably dimethyl sulfoxide), aromatic hydrocarbons (preferably benzene Or toluene) or a halo having 1 to 10 carbon atoms and 1 to 10 halogen atoms. Lucans (preferably dichloromethane) may be included, but are not limited thereto. Not something. Preferred reaction temperatures range from -250C to 100C. The compound of formula (23) is reacted with an inert solvent at a reaction temperature in the range of -80C to 250C. With or without a base, with or without a base, a compound of formula $\text{R}^{\text{Three}}\text{H}$ (where R^{Three} is as defined above, except that SH, COR^7 , CO_2R^7 , Aryl and f Reacts with a compound of formula (1) to form a compound of formula (1) it can. Bases include alkali metal hydrides (preferably sodium hydride), Alkali metal alkoxides (C1-6) (preferably sodium methoxy) Or sodium ethoxide), alkaline earth metal hydrides, alkali metals Diakylamides (preferably lithium di-isopropylamide), alkali Metal carbonates, alkali metal bicarbonates, alkali metal bis (trialkyl lyf) amides (preferably sodium bis (trimethylsilyl) amide), Liakylamines (preferably N, N-di-isopropyl-N-ethylamido)) Or aromatic amines (preferably pyridine). It is not limited. As the inert solvent, alkyl alcohols (C 1 to C 1) 8, preferably methanol or ethanol), lower alkanenitrile (charcoal) Prime numbers 1 to 6, preferably acetonitrile, dialkyl ethers (preferably Diethyl ether), cyclic ethers (preferably tetrahydrofuran or , 4-dioxane), N, N-dialkylformamides (preferably dimethyl E Lumamide), N, N-dialkylacetamides (preferably dimethylacetamide) Amide), cyclic amides (preferably N-methylpyrrolidin-2-one), dia Alkyl sulfoxides (preferably dimethyl sulfoxide), aromatic hydrocarbons (Preferably benzene or toluene) or 1 to 10 charcoal and halogen Haloalkanes having 1 to 10 atoms (preferably dichloromethane) may be included. However, it is not limited to them. Preferred reaction temperatures are in the range of 0 ° C to 140 ° C. It is an enclosure. Some compounds of formula (1) can also be prepared using the method shown in Scheme 15. You.

Scheme 15 Formula (24) (where R_2 is a lower alkyl group, and Ar is as defined above, is reacted with hydrazine in the presence or absence of an inert solvent To give an intermediate of formula (25) wherein Ar is as defined above, be able to. The conditions were as follows: in Scheme 4, an intermediate of formula (4) was prepared from a compound of formula (3). The conditions are the same as those used for manufacturing. A compound of the formula (25) (where A is N): The formula R in an inert solvent, with or without the presence of an acid, $\text{C}(\text{NH})\text{OR}_2$ (Where R^1 is as defined above, and R_2 is a lower alkyl group) And then in an inert solvent, with or without the presence of a base, the formula $\text{Y} = \text{C}(\text{R}_2)_2$ (Wherein Y is O or S_{Three} is halogen (preferably chlorine), alkoxyl Reaction with a compound having 1 to 4 carbon atoms or alkylthio (1 to 4 carbon atoms) To give a compound of formula (27), wherein A is N and Y is O, S. Can be The conditions for these conversions are as follows: in Scheme 4, the compound of formula (4) is converted to the compound of formula (7) This is the same as the condition used to convert to. Alternatively, the compound of formula (21) can be converted to a compound of formula (22) in Scheme 14. Using the same conditions as those used in the case of substituting, equation (25) (where A is CR The compound of formula $\text{R}^1(\text{C} = \text{O})\text{CHR}(\text{C} = \text{Y})\text{OR}_2$ (Where R^1 And R is above R as defined above, R_2 is a lower alkyl group) And a compound of formula (27) wherein A is CR. Equation (27) (where, Y is O) in an inert solvent with or without the presence of a base. Treatment with a fluorinating or sulfonylating agent and then the presence of a base in an inert solvent. With or without $\text{R}^{\text{Three}}\text{H}$ or $\text{R}^{\text{Two}}\text{H}$ By reacting with H, formula (1) (wherein Z is CR^{Two}) is obtained. As will be appreciated by those skilled in the art, to obtain compounds of formula (1) And halogenating agent, sulfonylating agent, $\text{R}^{\text{Three}}\text{H}$ or $\text{R}^{\text{Two}}\text{H}$ Various combinations of can be used. For example, in some cases, Reacting with a stoichiometric amount of a halogenating or sulfonylating agent to form $\text{R}^{\text{Two}}\text{H}$ (or $\text{R}^{\text{Three}}\text{H}$) And then the reaction with the halogenating or sulfonylating agent is repeated, Ran: $\text{R}^{\text{Three}}\text{H}$ (or $\text{R}^{\text{Two}}\text{H}$) to give a compound of formula (1) Sometimes. The reaction conditions and reagents used for these transformations are described in Scheme 14 (A is CR), the compound of the formula (22) is replaced with the compound of the formula (23) and further the compound of the formula (1) When converted to a compound, or in Scheme 1 (where A is N) The method used to convert the compound into a compound of formula (8) and further a compound of formula (1) Same as the case. Alternatively, the compound of formula (27) in Scheme 15 wherein Y is S it can also be converted to a compound of the formula (1). Inert intermediate compound of formula (27) R in the solvent R^1X (where R^1 is lower alkyl, X is halogen, alkanesulfonyl Oxy or haloalkanesulfonyloxy) (Then, optionally, oxidized with an oxidizing agent in an inert solvent) in a medium, R with or without the presence of a base Three By reacting with H, the formula (1)) is obtained. The reaction conditions and reagents used are represented by the formula (7) The intermediate compound is a compound of the formula (12) (or the formula (13)) and further a compound of the formula (1) The conditions are the same as those used to convert the compound. Compounds of formula (1) can be prepared using the alternative route shown in scheme 15 R can be made from a compound. The compound of formula (24) can be prepared by reacting the compound of formula (3) Used to convert the compound into a compound of the formula (17) and further a compound of the formula (7) With the presence of the formula NH in an inert solvent, with or without the presence of an acid, $\text{NH}(\text{C} = \text{NH})\text{NH}_2$ With a compound of formula $\text{R}^1\text{C}(\text{OR}_2)_2$ (Where R_2 is lower alk, R^1 is as defined above) via a reaction with a compound of formula (27)). Some compounds of formula (2) can be prepared by the method illustrated in Scheme 16. Wear.

Scheme 16 A compound of formula (27b) is prepared by reacting the compound of formula (27b) with or without a base in an inert solvent. R^1X (where R^1 is as defined above, X is halogen, alkane sulfone Various alkylations of carbonyloxy or haloalkanesulfonyloxy) When treated with the agent, the structure of formula (28) is obtained. Formula (28) (where Y is O) In an inert solvent with or without the presence of a base. Or a sulfonylating agent, followed by the presence of a base in an inert solvent, or R without Three When reacted with H, the compound of formula (2) is obtained. Reaction of these transformations The conditions are as follows: Scheme 14 (when A is CR) converts a compound of formula (22) into a compound of formula (23). When converting to a compound, further to a compound of formula (1), or Scheme 1 (where A is N), the compound of formula (7) is converted to a compound of formula (8), and further a compound of formula (1) This is the same as the condition used when converting to. Alternatively, a compound of formula (28) wherein Y is S in an inert solvent R^1X (where R^1 is lower alkyl, X is halogen, alkanesulfonyl Oxy or haloalkanesulfonyloxy), it is then optionally oxidized with an oxidizing agent in an inert solvent, in the presence or absence of a base Three By reacting with H, the formula (1) is obtained. The reaction conditions and reagents to be used are as shown in Scheme 2 The intermediate compound is a compound of formula (12) (or formula (13)) and a compound of formula (1) The conditions are the same as those used for the conversion into the product. Compounds of formula (1) wherein Z is CDH are illustrated in Scheme 16. Thus, it can be converted to the compound of the formula (2). The presence of a base in an inert solvent, Formula R^1X (where R^1 is as defined above, X is halogen, Alkanesulfonyloxy or haloalkanesulfonyloxy) The structure of (2) is obtained by treating with the alkylating agent. Recognized by those skilled in the art As described above, the method used in Scheme 16 is based on the formula (1) (where Z is CCR^1 is) It can also be used to produce compounds. In the case of Scheme 16, the terms "base" and "inert solvent" have the following meanings Can be

provided. Bases include alkali metal hydrides (preferably hydrogenated Sodium), alkali metal alkoxides (C1-6) (preferably n-Butyl lithium methoxide or sodium ethoxide), alkaline earth metal hydrides, Alkali metal dialkylamides (preferably lithium di-isopropylamide), Alkali metal bis (trialkylsilyl) amides (preferably sodium MBis (trimethylsilyl) amide), trialkylamines (preferably N, N-di-isopropyl-N-ethylamine or triethylamine) or Aromatic amines (preferably pyridine) may be included, but are not limited thereto. Not. Inert solvents include lower alkane nitriles (C1-6, 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 MI (Preferably N-methylpyrrolidin-2-one), dialkyl sulfoxide (Preferably dimethyl sulfoxide), aromatic hydrocarbons (preferably benzene) Halo having 1 to 10 carbon atoms and 1 to 10 halogen atoms. Lowboans (preferably dichloromethane) may be included, but are not limited thereto. It is not something to be done. Preferred reaction temperatures range from -20C to 100C. Example Analytical data was recorded for the compounds described below using the following general method. Step Roton NMR spectra were recorded on an IBM-Bruker FTNMR (300 MHz). Conversion Chemical shifts in deuterated chloroform or deuterated dimethyl sulfoxide specified below. Was recorded using ppm (δ) based on the internal standard tetramethylsilane. quality Quantitative spectra (MS) or high-resolution mass spectra (HRMS) are available from Finnegan MAT 8230 spectrometer (using ammonia as carrier gas as specified below) Using chemical ionization (CI) or gas chromatography (GC) or Recorded on a Hewlett Packard Model 5988A spectrometer. Melting point is Buchi Model 510 melting point measuring instrument And recorded without correction. Boiling points are uncorrected. PH measurement during the reaction PH test paper. Reagents are purchased from commercial sources, and if necessary Perrin and W.L.F. Armarego, experiment Purification of Laboratory Chemicals, 3rd edition, (New York, Ferg amon Press, 1988) and purified prior to use according to the general method outlined. Black Matography was performed on silica gel using the solvent system indicated below. Mixed solvent in the case of a system, the volume ratio is indicated. Otherwise, parts and percentages are based on weight. The following examples describe the invention in more detail. Examples of these Describes the best means currently conceivable for carrying out the invention, and They are provided for illustrative purposes only and do not limit the invention.

Example 1 2,7-dimethyl-8-(2,4-dimethylphenyl) [1,5-a]-pyrazolo Production of b-[1,3,5]-triazin-4 (3H)-one (Equation 7, where Y is O, R¹ is CH₃, R² is CH₃, Z is C-CH₃, Ar is 2,4-dimethyl Phenyl) A. 1-cyano-1-(2,4-dimethylphenyl) propan-2-one Sodium pellet (9.8 g, 0.43 mol) was added to 2,4-dimethylphenyl A solution of luacetanitrile (48 g, 0.33 mol) in ethyl acetate (150 mL) in portions at ambient temperature. Heat the reaction mixture to reflux temperature and stir for 16 hours. The resulting suspension was cooled to room temperature and filtered. A large amount of ether And air dried. Dissolve the solid in water and add 1N HCl solution to pH = 5 To 6. The mixture was extracted with ethyl acetate (3 x 200 mL). Combine organic layers MgSO₄ And filtered. Evaporation of the solvent under reduced pressure gave a white solid (45.7 g, 74% yield). NMR (CDCl₃, 300 MHz): 7.18 (s, 1H), 6.8 (s, 1H), 6.5 (s, 1H), 6.3 (s, 1H), 6.2 (s, 1H), 6.1 (s, 1H), 5.9 (s, 1H), 5.8 (s, 1H), 5.7 (s, 1H), 5.6 (s, 1H), 5.5 (s, 1H), 5.4 (s, 1H), 5.3 (s, 1H), 5.2 (s, 1H), 5.1 (s, 1H), 5.0 (s, 1H), 4.9 (s, 1H), 4.8 (s, 1H), 4.7 (s, 1H), 4.6 (s, 1H), 4.5 (s, 1H), 4.4 (s, 1H), 4.3 (s, 1H), 4.2 (s, 1H), 4.1 (s, 1H), 4.0 (s, 1H), 3.9 (s, 1H), 3.8 (s, 1H), 3.7 (s, 1H), 3.6 (s, 1H), 3.5 (s, 1H), 3.4 (s, 1H), 3.3 (s, 1H), 3.2 (s, 1H), 3.1 (s, 1H), 3.0 (s, 1H), 2.9 (s, 1H), 2.8 (s, 1H), 2.7 (s, 1H), 2.6 (s, 1H), 2.5 (s, 1H), 2.4 (s, 1H), 2.3 (s, 1H), 2.2 (s, 1H), 2.1 (s, 1H), 2.0 (s, 1H), 1.9 (s, 1H), 1.8 (s, 1H), 1.7 (s, 1H), 1.6 (s, 1H), 1.5 (s, 1H), 1.4 (s, 1H), 1.3 (s, 1H), 1.2 (s, 1H), 1.1 (s, 1H), 1.0 (s, 1H), 0.9 (s, 1H), 0.8 (s, 1H), 0.7 (s, 1H), 0.6 (s, 1H), 0.5 (s, 1H), 0.4 (s, 1H), 0.3 (s, 1H), 0.2 (s, 1H), 0.1 (s, 1H). CI-MS: 202 (M + H). C. 5-acetamidino-4-(2,4-dimethylphenyl) -3-methylpyrazole Potassium carbonate (59.5 g, 0.50 mol), dichloromethane (120 mL) And water (350 mL) while stirring vigorously with ethylacetamide Salt hydrochloride (50 g, 0.48 mol) was added quickly. Separate the two layers and separate the aqueous layer. Extracted with dichloromethane (2 x 120 mL). Combine the organic layers and add MgSO₄ And filtered. The solvent is distilled off by atmospheric distillation to obtain a clear pale yellow liquid. The residue in the vessel (35.0 g) was used without further purification. 5-amino-4-(2,4-dimethylphenyl) -3-methylpyrazole (3.4 g, 0.17 mol), ethylacetimidate (22 g, 0.25 mol) And a mixture of acetonitrile (500 mL) was stirred while glacial acetic acid (9.7 mL, 0.17 mol) was added. The resulting reaction mixture was stirred at room temperature for 3 days. After the stirring, the solution was concentrated under reduced pressure to about one third of the initial volume. Filter the resulting suspension. And the collected solid was washed with copious amounts of ether. The white solid was dried under reduced pressure (31.4 g, 61% yield). NMR (DMSO-d₆, 300 MHz): 7.00 (s, 1H), 6.90 (dd, 2H, J = 7, 1), 2.28 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.81 (s, 3H). CI-MS: 243 (M + H). D. 2,7-dimethyl-8-(2,4-dimethylphenyl) [1,5-a]-Pyrazolo-[1,3,5]-triazin-4 (3H)-one The sodium pellet (23 g, 1 mol) was stirred vigorously with ethanol (50 mL). After all the sodium has reacted, No-4-(2,4-dimethylphenyl) -3-methylpyrazole, acetate (31.2 g, 0.1 mol) and diethyl carbonate (97 mL, 0.8 mol) Was. The resulting reaction mixture was heated to reflux and stirred for 18 hours. Mix room Warm And the solvent was distilled off under reduced pressure. Dissolve the residue in water and slowly add 1N HCl solution pH = 5-6. The aqueous layer was extracted three times with ethyl acetate. Combine organic layers MgSO₄ And filtered. When the solvent is distilled off under reduced pressure, a light tan solid is obtained. Obtained (26 g, 98% yield). NMR (CDCl₃, 300 MHz): 7.15 (s, 1H), 7.09 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H). CI-MS: 269 (M + H).

Example 2 5-methyl-3-(2,4,6-trimethylphenyl) [1,5-a]-[1,3,5]-triazin-7 (6H)-one (Equation 7, where Y is O, R¹ is CH₃, R² is CH₃, Z is N, Ar is 2,4,6-trimethylphenyl Hentl) A. 1-phenylmethyl-4-(2,4,6-trimethylphenyl) -5-a Minotriazole 2,4,6-trimethylbenzyl cyanide (1.0 g, 6.3 mmol), Benzyl dichloride (0.92 g, 6.9 mmol) and potassium t-butoxide ((0.78 g, 6.9 mmol) in tetrahydrofuran (10 mL) The material was stirred at ambient temperature for 2.5 days. Dilute the resulting suspension with water and add ethyl acetate. Extracted three times. Combine the organic layers and add MgSO₄ And filtered. Decompress the solvent. Evaporation gave a brown oil. This is crushed with ether and filtered to yellow. Was obtained (1.12 g, yield 61%). NMR (CDCl₃, 300 MHz): 7.60 to 7.30 (m, 5H), 7.30 to 7.20 (m, 2H), 5.50 (s, 2H), 5.18 (broad s, 2H), 2.30 (s, 3H), 2.10 (s, 6H). CI-MS: 293 (M + H). B. 4-(2,4,6-trimethylphenyl) -5-aminotriazole Liquid ammonia (30 mL) and 1-phenylmethyl-4-(2,4,6-trimethylphenyl) -5-aminotriazole (1.1 g, 3.8 mmol) To a mixture of was added sodium (500 mg, 22 mmol) with stirring. The reaction mixture was stirred until a dark green color persisted. Ammonium chloride solution (mL) The mixture was stirred for 16 hours while warming to ambient temperature. The residue was treated with 1M HCl. Filtered. The aqueous layer was basified with concentrated aqueous ammonia (pH = 9), and three times with ethyl acetate. Extracted. Combine the organic layers and add MgSO₄ And filtered. Remove the solvent under reduced pressure. Gave a single yellow solid by thin layer chromatography (ethyl acetate) (520 mg). NMR (CDCl₃, 300 MHz): 6.97 (s, 2H), 3.68-3.50 (broad s, 2H), 2.32 (s, 3H), 2.10 (s, 6H). CI-MS: 203 (M + H). C. 4-(2,4,6-trimethylphenyl) -5-acetamidino-4-aminotriazole, Acetate 4-(2,4,6-trimethylphenyl) -5-aminotriazole (400 mg, 1.98 mmol), ethylacetimidate (261 mg, 3 mmol) And glacial acetic acid (0.1 mL, 1.98 mmol) in acetonitrile (6 mL) The solution was stirred at ambient temperature for 4 hours. The resulting suspension is filtered and the collected solids are And washed with ether. Drying under reduced pressure gave a white solid (490 mg, yield 82%). NMR (DMSO-d₆, 300 MHz): 7.90 to 7.70 (broad s, 0.5H), 7.50 to 7.20 (broad s, 0.5H), 6.90 (s, 2H), 3.50-3.10 (broad s, 3H), 2.30 to 2.20 (broad s, 3H), 2.05 (d, 1H, J = 7), 1.96 (s, 6H), 1.87 (s, 6H). CI-MS: 244 (M + H). D. 5-methyl-3-(2,4,6-trimethylphenyl) [1,5-a]-[1,2,3]-Triazolo-[1,3,5]-triazin-7 (4H)-one Sodium (368 mg, 16.2 mmol) in ethanol (10 mL) It was added with stirring at warm. After the reaction of sodium, 4-(2,4,6-trimethylphenyl) -5-acetamidino-4-aminotriazole, acetate (490 mg, 1.6 mmol) and diethyl carbonate (1.6 mL, 13 mmol) were added. reaction The mixture was stirred at reflux for 5 hours, then cooled to room temperature. The reaction mixture with water Dilute, add 1N HCl solution to pH = 5-6, extract with ethyl acetate. Performed three times. Combine the organic layers and add MgSO₄ And filtered. The solvent is distilled off under reduced pressure. This gave a yellow residue. Titration with ether and filtration gave a yellow solid. (300 mg, 59% yield). NMR (CDCl₃, 300 MHz): 6.98 (s, 2H), 2.65 (s, 3H), 2.35 (s, 3H), 2.10 (s, 6H). CI-MS: 270 (M + H).

Example 3 4-(di (carbomethoxy) methyl) -2,7-dimethyl-8-(2,4-dimethyl Preparation of [1,5-a]-pyrazolo-[1,3,5]-triazine (Formula 1, where R¹ is CH₃, R² is CH₃, R³ is CH₃, R⁴ is CH₃, R⁵ is CH₃, R⁶ is CH₃, R⁷ is CH₃, R⁸ is CH₃, R⁹ is CH₃, R¹⁰ is CH₃, R¹¹ is CH₃, R¹² is CH₃, R¹³ is CH₃, R¹⁴ is CH₃, R¹⁵ is CH₃, R¹⁶ is CH₃, R¹⁷ is CH₃, R¹⁸ is CH₃, R¹⁹ is CH₃, R²⁰ is CH₃, R²¹ is CH₃, R²² is CH₃, R²³ is CH₃, R²⁴ is CH₃, R²⁵ is CH₃, R²⁶ is CH₃, R²⁷ is CH₃, R²⁸ is CH₃, R²⁹ is CH₃, R³⁰ is CH₃, R³¹ is CH₃, R³² is CH₃, R³³ is CH₃, R³⁴ is CH₃, R³⁵ is CH₃, R³⁶ is CH₃, R³⁷ is CH₃, R³⁸ is CH₃, R³⁹ is CH₃, R⁴⁰ is CH₃, R⁴¹ is CH₃, R⁴² is CH₃, R⁴³ is CH₃, R⁴⁴ is CH₃, R⁴⁵ is CH₃, R⁴⁶ is CH₃, R⁴⁷ is CH₃, R⁴⁸ is CH₃, R⁴⁹ is CH₃, R⁵⁰ is CH₃, R⁵¹ is CH₃, R⁵² is CH₃, R⁵³ is CH₃, R⁵⁴ is CH₃, R⁵⁵ is CH₃, R⁵⁶ is CH₃, R⁵⁷ is CH₃, R⁵⁸ is CH₃, R⁵⁹ is CH₃, R⁶⁰ is CH₃, R⁶¹ is CH₃, R⁶² is CH₃, R⁶³ is CH₃, R⁶⁴ is CH₃, R⁶⁵ is CH₃, R⁶⁶ is CH₃, R⁶⁷ is CH₃, R⁶⁸ is CH₃, R⁶⁹ is CH₃, R⁷⁰ is CH₃, R⁷¹ is CH₃, R⁷² is CH₃, R⁷³ is 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CH₃, R³⁰⁷ is CH₃, R³⁰⁸ is CH₃, R³⁰⁹ is CH₃, R³¹⁰ is CH₃, R³¹¹ is CH₃, R³¹² is CH₃, R³¹³ is CH₃, R³¹⁴ is CH₃, R³¹⁵ is CH₃, R³¹⁶ is CH₃, R³¹⁷ is CH₃, R³¹⁸ is CH₃, R³¹⁹ is CH₃, R³²⁰ is CH₃, R³²¹ is CH₃, R³²² is CH₃, R³²³ is CH₃, R³²⁴ is CH₃, R³²⁵ is CH₃, R³²⁶ is CH₃, R³²⁷ is CH₃, R³²⁸ is CH₃, R³²⁹ is CH₃, R³³⁰ is CH₃, R³³¹ is CH₃, R³³² is CH₃, R³³³ is CH₃, R³³⁴ is CH₃, R³³⁵ is CH₃, R³³⁶ is CH₃, R³³⁷ is CH₃, R³³⁸ is CH₃, R³³⁹ is CH₃, R³⁴⁰ is CH₃, R³⁴¹ is CH₃, R³⁴² is CH₃, R³⁴³ is CH₃, R³⁴⁴ is CH₃, R³⁴⁵ is CH₃, R³⁴⁶ is CH₃, R³⁴⁷ is CH₃, R³⁴⁸ is CH₃, R³⁴⁹ is CH₃, R³⁵⁰ is CH₃, R³⁵¹ is CH₃, R³⁵² is CH₃, R³⁵³ is CH₃, R³⁵⁴ is CH₃, R³⁵⁵ is CH₃, R³⁵⁶ is CH₃, R³⁵⁷ is CH₃, R³⁵⁸ is CH₃, R³⁵⁹ is CH₃, R³⁶⁰ is CH₃, R³⁶¹ is CH₃, R³⁶² is CH₃, R³⁶³ is CH₃, R³⁶⁴ is CH₃, R³⁶⁵ is CH₃, R³⁶⁶ is CH₃, R³⁶⁷ is CH₃, R³⁶⁸ is CH₃, R³⁶⁹ is CH₃, R³⁷⁰ is CH₃, R³⁷¹ is CH₃, R³⁷² is CH₃, R³⁷³ is CH₃, R³⁷⁴ is CH₃, R³⁷⁵ is CH₃, R³⁷⁶ is CH₃, R³⁷⁷ is CH₃, R³⁷⁸ is CH₃, R³⁷⁹ is CH₃, R³⁸⁰ is CH₃, R³⁸¹ is CH₃, R³⁸² is CH₃, R³⁸³ is CH₃, R³⁸⁴ is CH₃, R³⁸⁵ is CH₃, R³⁸⁶ is CH₃, R³⁸⁷ is CH₃, R³⁸⁸ is CH₃, R³⁸⁹ is CH₃, R³⁹⁰ is CH₃, R³⁹¹ is CH₃, R³⁹² is CH₃, R³⁹³ is CH₃, R³⁹⁴ is CH₃, R³⁹⁵ is CH₃, R³⁹⁶ is CH₃, R³⁹⁷ is CH₃, R³⁹⁸ is CH₃, R³⁹⁹ is CH₃, R⁴⁰⁰ is CH₃, R⁴⁰¹ is CH₃, R⁴⁰² is CH₃, R⁴⁰³ is CH₃, R⁴⁰⁴ is CH₃, R⁴⁰⁵ is CH₃, R⁴⁰⁶ is CH₃, R⁴⁰⁷ is CH₃, R⁴⁰⁸ is CH₃, R⁴⁰⁹ is CH₃, R⁴¹⁰ is CH₃, R⁴¹¹ is CH₃, R⁴¹² is CH₃, R⁴¹³ is CH₃, R⁴¹⁴ is CH₃, R⁴¹⁵ is CH₃, R⁴¹⁶ is CH₃, R⁴¹⁷ is CH₃, R⁴¹⁸ is CH₃, R⁴¹⁹ is CH₃, R⁴²⁰ is CH₃, R⁴²¹ is CH₃, R⁴²² is CH₃, R⁴²³ is CH₃, R⁴²⁴ is CH₃, R⁴²⁵ is CH₃, R⁴²⁶ is CH₃, R⁴²⁷ is CH₃, R⁴²⁸ is CH₃, R⁴²⁹ is CH₃, R⁴³⁰ is CH₃, R⁴³¹ is CH₃, R⁴³² is CH₃, R⁴³³ is CH₃, R⁴³⁴ is CH₃, R⁴

1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CHMS: 327 (M + H). B. 4- (di (carbomethoxy) methyl)-2,7-dimethyl-8- (2,4-dimethylphenyl) [1,5-a]-pyrazolo-1,3,5-triazine Sodium hydride (80 mg in 60% oil, while discarding hexane for each washing). 2 mmol) was washed twice with hexane and dried in anhydrous tetrahydrofuran (THF; 1 mL). Diethyl malonate (0.32 g, 2 mmol) in THF (2 mL) solution was added dropwise over 5 minutes. During that time, vigorous gas evolution occurred. 4-chloro-2,7-dimethyl-8- (2,4-dichlorophenyl) [1,5-a]-pyra A solution of azolotriazine (0.5 g, 1.75 mmol) in THF (2 mL) was added. The reaction mixture was stirred for 48 hours under a nitrogen atmosphere. Pour the resulting suspension into water. Extracted three times with ethyl acetate. The organic layers were combined, washed once with brine, and dried over $MgSO_4$. And filtered. The solvent was distilled off under reduced pressure to obtain a brown oil. Column chromatography Perform chromatography (ethyl acetate: hexane :: 1: 9) and evaporate the solvent under reduced pressure. And a pale yellow solid was obtained (Rf = 0.2, 250 mg, yield 55%). Melting point 50-52 [deg.] C. NMR ($CDCl_3$, 300 MHz): 12.35 (broad s, 1H), 7.15 to 7.00 (m, 3H), 4.40 (q, 2H, J = 7), 4.30 (q, 2H, J = 7), 2.4, 2.35, 2.3, 2.2, 2.1 (5s, 12H) 1.4 (t, 3H, J = 7), 1.35-1.25 (m, 3H); CH-MS: Calculated value: 411.2023, Observed value: 411.223.

Example 6 4- (1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8- (2,4-dichlorophenyl) [1,5-a]-pyrazolo-1,3,5-triazine Manufacturing (Formula 1, where R^{Thre} is NHCH (CH_2), R^1 is CH_2 , R^2 is CH_2 , R^3 is CH_2 , R^4 is CH_2 , R^5 is CH_2 , R^6 is CH_2 , R^7 is CH_2 , R^8 is CH_2 , R^9 is CH_2 , R^{10} is CH_2 , R^{11} is CH_2 , R^{12} is CH_2 , R^{13} is CH_2 , R^{14} is CH_2 , R^{15} is CH_2 , R^{16} is CH_2 , R^{17} is CH_2 , R^{18} is CH_2 , R^{19} is CH_2 , R^{20} is CH_2 , R^{21} is CH_2 , R^{22} is CH_2 , R^{23} is CH_2 , R^{24} is CH_2 , R^{25} is CH_2 , R^{26} is CH_2 , R^{27} is CH_2 , R^{28} is CH_2 , R^{29} is CH_2 , R^{30} is CH_2 , R^{31} is CH_2 , R^{32} is CH_2 , R^{33} is CH_2 , R^{34} is CH_2 , R^{35} is CH_2 , R^{36} is CH_2 , R^{37} is CH_2 , R^{38} is CH_2 , R^{39} is CH_2 , R^{40} is CH_2 , R^{41} is CH_2 , R^{42} is CH_2 , R^{43} is CH_2 , R^{44} is CH_2 , R^{45} is CH_2 , R^{46} is CH_2 , R^{47} is CH_2 , R^{48} is CH_2 , R^{49} is CH_2 , R^{50} is CH_2 , R^{51} is CH_2 , R^{52} is CH_2 , R^{53} is CH_2 , R^{54} is CH_2 , R^{55} is CH_2 , R^{56} is CH_2 , R^{57} is CH_2 , R^{58} is CH_2 , R^{59} is CH_2 , R^{60} is CH_2 , R^{61} is CH_2 , R^{62} is CH_2 , R^{63} is CH_2 , R^{64} is CH_2 , R^{65} is CH_2 , R^{66} is CH_2 , R^{67} is CH_2 , R^{68} is CH_2 , R^{69} is CH_2 , R^{70} is CH_2 , R^{71} is CH_2 , R^{72} is CH_2 , R^{73} is CH_2 , R^{74} is CH_2 , R^{75} is CH_2 , R^{76} is CH_2 , R^{77} is CH_2 , R^{78} is CH_2 , R^{79} is CH_2 , R^{80} is CH_2 , R^{81} is CH_2 , R^{82} is CH_2 , R^{83} is CH_2 , R^{84} is CH_2 , R^{85} is CH_2 , R^{86} is CH_2 , R^{87} is CH_2 , R^{88} is CH_2 , R^{89} is CH_2 , R^{90} is CH_2 , R^{91} is CH_2 , R^{92} is CH_2 , R^{93} is CH_2 , R^{94} is CH_2 , R^{95} is CH_2 , R^{96} is CH_2 , R^{97} is CH_2 , R^{98} is CH_2 , R^{99} is CH_2 , R^{100} is CH_2 , R^{101} is CH_2 , R^{102} is CH_2 , R^{103} is CH_2 , R^{104} is CH_2 , R^{105} is CH_2 , R^{106} is CH_2 , R^{107} is CH_2 , R^{108} is CH_2 , R^{109} is CH_2 , R^{110} is CH_2 , R^{111} is CH_2 , R^{112} is CH_2 , R^{113} is CH_2 , R^{114} is CH_2 , R^{115} is CH_2 , R^{116} is CH_2 , R^{117} is CH_2 , R^{118} is CH_2 , R^{119} is CH_2 , R^{120} is CH_2 , R^{121} is CH_2 , R^{122} is CH_2 , R^{123} is CH_2 , R^{124} is CH_2 , R^{125} is CH_2 , R^{126} is CH_2 , R^{127} is CH_2 , R^{128} is CH_2 , R^{129} is CH_2 , R^{130} is CH_2 , R^{131} is CH_2 , R^{132} is CH_2 , R^{133} is CH_2 , R^{134} is CH_2 , R^{135} is CH_2 , R^{136} is CH_2 , R^{137} is CH_2 , R^{138} is CH_2 , R^{139} is CH_2 , R^{140} is CH_2 , R^{141} is CH_2 , R^{142} is CH_2 , R^{143} is CH_2 , R^{144} is CH_2 , R^{145} is CH_2 , R^{146} is CH_2 , R^{147} is CH_2 , R^{148} is CH_2 , R^{149} is CH_2 , R^{150} is CH_2 , R^{151} is CH_2 , R^{152} is CH_2 , R^{153} is CH_2 , R^{154} is CH_2 , R^{155} is CH_2 , R^{156} is CH_2 , R^{157} is CH_2 , R^{158} is CH_2 , R^{159} is CH_2 , R^{160} is CH_2 , R^{161} is CH_2 , R^{162} is CH_2 , R^{163} is CH_2 , R^{164} is CH_2 , R^{165} is CH_2 , R^{166} is CH_2 , R^{167} is CH_2 , R^{168} is CH_2 , R^{169} is CH_2 , R^{170} is CH_2 , R^{171} is CH_2 , R^{172} is CH_2 , R^{173} is CH_2 , R^{174} is CH_2 , R^{175} is CH_2 , R^{176} is CH_2 , R^{177} is CH_2 , R^{178} is CH_2 , R^{179} is CH_2 , R^{180} is CH_2 , R^{181} is CH_2 , R^{182} is CH_2 , R^{183} is CH_2 , R^{184} is CH_2 , R^{185} is CH_2 , R^{186} is CH_2 , R^{187} is CH_2 , R^{188} is CH_2 , R^{189} is CH_2 , R^{190} is CH_2 , R^{191} is CH_2 , R^{192} is CH_2 , R^{193} is CH_2 , R^{194} is CH_2 , R^{195} is CH_2 , R^{196} is CH_2 , R^{197} is CH_2 , R^{198} is CH_2 , R^{199} is CH_2 , R^{200} is CH_2 , R^{201} is CH_2 , R^{202} is CH_2 , R^{203} is CH_2 , R^{204} is CH_2 , R^{205} is CH_2 , R^{206} is CH_2 , R^{207} is CH_2 , R^{208} is CH_2 , R^{209} is CH_2 , R^{210} is CH_2 , R^{211} is CH_2 , R^{212} is CH_2 , R^{213} is CH_2 , R^{214} is CH_2 , R^{215} is CH_2 , R^{216} is CH_2 , R^{217} is CH_2 , R^{218} is CH_2 , R^{219} is CH_2 , R^{220} is CH_2 , R^{221} is CH_2 , R^{222} is CH_2 , R^{223} is CH_2 , R^{224} is CH_2 , R^{225} is CH_2 , R^{226} is CH_2 , R^{227} is CH_2 , R^{228} is CH_2 , R^{229} is CH_2 , R^{230} is CH_2 , R^{231} is CH_2 , R^{232} is CH_2 , R^{233} is CH_2 , R^{234} is CH_2 , R^{235} is CH_2 , R^{236} is CH_2 , R^{237} is CH_2 , R^{238} is CH_2 , R^{239} is CH_2 , R^{240} is CH_2 , R^{241} is CH_2 , R^{242} is CH_2 , R^{243} is CH_2 , R^{244} is CH_2 , R^{245} is CH_2 , R^{246} is CH_2 , R^{247} is CH_2 , R^{248} is CH_2 , R^{249} is CH_2 , R^{250} is CH_2 , R^{251} is CH_2 , R^{252} is CH_2 , R^{253} is CH_2 , R^{254} is CH_2 , R^{255} is CH_2 , R^{256} is CH_2 , R^{257} is CH_2 , R^{258} is CH_2 , R^{259} is CH_2 , R^{260} is CH_2 , R^{261} is CH_2 , R^{262} is CH_2 , R^{263} is CH_2 , R^{264} is CH_2 , R^{265} is CH_2 , R^{266} is CH_2 , R^{267} is CH_2 , R^{268} is CH_2 , R^{269} is CH_2 , R^{270} is CH_2 , R^{271} is CH_2 , R^{272} is CH_2 , R^{273} is CH_2 , R^{274} is CH_2 , R^{275} is CH_2 , R^{276} is CH_2 , R^{277} is CH_2 , R^{278} is CH_2 , R^{279} is CH_2 , R^{280} is CH_2 , R^{281} is CH_2 , R^{282} is CH_2 , R^{283} is CH_2 , R^{284} is CH_2 , R^{285} is CH_2 , R^{286} is CH_2 , R^{287} is CH_2 , R^{288} is CH_2 , R^{289} is CH_2 , R^{290} is CH_2 , R^{291} is CH_2 , R^{292} is CH_2 , R^{293} is CH_2 , R^{294} is CH_2 , R^{295} is CH_2 , R^{296} is CH_2 , R^{297} is CH_2 , R^{298} is CH_2 , R^{299} is CH_2 , R^{300} is CH_2 , R^{301} is CH_2 , R^{302} is CH_2 , R^{303} is CH_2 , R^{304} is CH_2 , R^{305} is CH_2 , R^{306} is CH_2 , R^{307} is CH_2 , R^{308} is CH_2 , R^{309} is CH_2 , R^{310} is CH_2 , R^{311} is CH_2 , R^{312} is CH_2 , R^{313} is CH_2 , R^{314} is CH_2 , R^{315} is CH_2 , R^{316} is CH_2 , R^{317} is CH_2 , R^{318} is CH_2 , R^{319} is CH_2 , R^{320} is CH_2 , R^{321} is CH_2 , R^{322} is CH_2 , R^{323} is CH_2 , R^{324} is CH_2 , R^{325} is CH_2 , R^{326} is CH_2 , R^{327} is CH_2 , R^{328} is CH_2 , R^{329} is CH_2 , R^{330} is CH_2 , R^{331} is CH_2 , R^{332} is CH_2 , R^{333} is CH_2 , R^{334} is CH_2 , R^{335} is CH_2 , R^{336} is CH_2 , R^{337} is CH_2 , R^{338} is CH_2 , R^{339} is CH_2 , R^{340} is CH_2 , R^{341} is CH_2 , R^{342} is CH_2 , R^{343} is CH_2 , R^{344} is CH_2 , R^{345} is CH_2 , R^{346} is CH_2 , R^{347} is CH_2 , R^{348} is CH_2 , R^{349} is CH_2 , R^{350} is CH_2 , R^{351} is CH_2 , R^{352} is CH_2 , R^{353} is CH_2 , R^{354} is CH_2 , R^{355} is CH_2 , R^{356} is CH_2 , R^{357} is CH_2 , R^{358} is CH_2 , R^{359} is CH_2 , R^{360} is CH_2 , R^{361} is CH_2 , R^{362} is CH_2 , R^{363} is CH_2 , R^{364} is CH_2 , R^{365} is CH_2 , R^{366} is CH_2 , R^{367} is CH_2 , R^{368} is CH_2 , R^{369} is CH_2 , R^{370} is CH_2 , R^{371} is CH_2 , R^{372} is CH_2 , R^{373} is CH_2 , R^{374} is CH_2 , R^{375} is CH_2 , R^{376} is CH_2 , R^{377} is CH_2 , R^{378} is CH_2 , R^{379} is CH_2 , R^{380} is CH_2 , R^{381} is CH_2 , R^{382} is CH_2 , R^{383} is CH_2 , R^{384} is CH_2 , R^{385} is CH_2 , R^{386} is CH_2 , R^{387} is CH_2 , R^{388} is CH_2 , R^{389} is CH_2 , R^{390} is CH_2 , R^{391} is CH_2 , R^{392} is CH_2 , R^{393} is CH_2 , R^{394} is CH_2 , R^{395} is CH_2 , R^{396} is CH_2 , R^{397} is CH_2 , R^{398} is CH_2 , R^{399} is CH_2 , R^{400} is CH_2 , R^{401} is CH_2 , R^{402} is CH_2 , R^{403} is CH_2 , R^{404} is CH_2 , R^{405} is CH_2 , R^{406} is CH_2 , R^{407} is CH_2 , R^{408} is CH_2 , R^{409} is CH_2 , R^{410} is CH_2 , R^{411} is CH_2 , R^{412} is CH_2 , R^{413} is CH_2 , R^{414} is CH_2 , R^{415} is CH_2 , R^{416} is CH_2 , R^{417} is CH_2 , R^{418} is CH_2 , R^{419} is CH_2 , R^{420} is CH_2 , R^{421} is CH_2 , R^{422} is CH_2 , R^{423} is CH_2 , R^{424} is CH_2 , R^{425} is CH_2 , R^{426} is CH_2 , R^{427} is CH_2 , R^{428} is CH_2 , R^{429} is CH_2 , R^{430} is CH_2 , R^{431} is CH_2 , R^{432} is CH_2 , R^{433} is CH_2 , R^{434} is CH_2 , R^{435} is CH_2 , R^{436} is CH_2 , R^{437} is CH_2 , R^{438} is CH_2 , R^{439} is CH_2 , R^{440} is CH_2 , R^{441} is CH_2 , R^{442} is CH_2 , R^{443} is CH_2 , R^{444} is CH_2 , R^{445} is CH_2 , R^{446} is CH_2 , R^{447} is CH_2 , R^{448} is CH_2 , R^{449} is CH_2 , R^{450} is CH_2 , R^{451} is CH_2 , R^{452} is CH_2 , R^{453} is CH_2 , R^{454} is CH_2 , R^{455} is CH_2 , R^{456} is CH_2 , R^{457} is CH_2 , R^{458} is CH_2 , R^{459} is CH_2 , R^{460} is CH_2 , R^{461} is CH_2 , R^{462} is CH_2 , R^{463} is CH_2 , R^{464} is CH_2 , R^{465} is CH_2 , R^{466} is CH_2 , R^{467} is CH_2 , R^{468} is CH_2 , R^{469} is CH_2 , R^{470} is CH_2 , R^{471} is CH_2 , R^{472} is CH_2 , R^{473} is CH_2 , R^{474} is CH_2 , R^{475} is CH_2 , R^{476} is CH_2 , R^{477} is CH_2 , R^{478} is CH_2 , R^{479} is CH_2 , R^{480} is CH_2 , R^{481} is CH_2 , R^{482} is CH_2 , R^{483} is CH_2 , R^{484} is CH_2 , R^{485} is CH_2 , R^{486} is CH_2 , R^{487} is CH_2 , R^{488} is CH_2 , R^{489} is CH_2 , R^{490} is CH_2 , R^{491} is CH_2 , R^{492} is CH_2 , R^{493} is CH_2 , R^{494} is CH_2 , R^{495} is CH_2 , R^{496} is CH_2 , R^{497} is CH_2 , R^{498} is CH_2 , R^{499} is CH_2 , R^{500} is CH_2 , R^{501} is CH_2 , R^{502} is CH_2 , R^{503} is CH_2 , R^{504} is CH_2 , R^{505} is CH_2 , R^{506} is CH_2 , R^{507} is CH_2 , R^{508} is CH_2 , R^{509} is CH_2 , R^{510} is CH_2 , R^{511} is CH_2 , R^{512} is CH_2 , R^{513} is CH_2 , R^{514} is CH_2 , R^{515} is CH_2 , R^{516} is CH_2 , R^{517} is CH_2 , R^{518} is CH_2 , R^{519} is CH_2 , R^{520} is CH_2 , R^{521} is CH_2 , R^{522} is CH_2 , R^{523} is CH_2 , R^{524} is CH_2 , R^{525} is CH_2 , R^{526} is CH_2 , R^{527} is CH_2 , R^{528} is CH_2 , R^{529} is CH_2 , R^{530} is CH_2 , R^{531} is CH_2 , R^{532} is CH_2 , R^{533} is CH_2 , R^{534} is CH_2 , R^{535} is CH_2 , R^{536} is CH_2 , R^{537} is CH_2 , R^{538} is CH_2 , R^{539} is CH_2 , R^{540} is CH_2 , R^{541} is CH_2 , R^{542} is CH_2 , R^{543} is CH_2 , R^{544} is CH_2 , R^{545} is CH_2 , R^{546} is CH_2 , R^{547} is CH_2 , R^{548} is CH_2 , R^{549} is CH_2 , R^{550} is CH_2 , R^{551} is CH_2 , R^{552} is CH_2 , R^{553} is CH_2 , R^{554} is CH_2 , R^{555} is CH_2 , R^{556} is CH_2 , R^{557} is CH_2 , R^{558} is CH_2 , R^{559} is CH_2 , R^{560} is CH_2 , R^{561} is CH_2 , R^{562} is CH_2 , R^{563} is CH_2 , R^{564} is CH_2 , R^{565} is CH_2 , R^{566} is CH_2 , R^{567} is CH_2 , R^{568} is CH_2 , R^{569} is CH_2 , R^{570} is CH_2 , R^{571} is CH_2 , R^{572} is CH_2 , R^{573} is CH_2 , R^{574} is CH_2 , R^{575} is CH_2 , R^{576} is CH_2 , R^{577} is CH_2 , R^{578} is CH_2 , R^{579} is CH_2 , R^{580} is CH_2 , R^{581} is CH_2 , R^{582} is CH_2 , R^{583} is

ml of tissue buffer. To After further centrifugation at 40,000 xg for 12 minutes, the pellet was Resuspend again until the protein concentration reaches 350 µg / ml and use for the assay. Binding assays were performed in 96-well plates, with a volume of each well of 300 µl. Add 50 µl of diluted test reagent (final concentration of drug is 10⁻¹⁰ to 10⁻¹⁵ M range) and 100 µl of ¹²⁵I-sheep-CRF (125I-CRF) (150 pM final concentration) and 150 µl of the cell homogenate. Next Then, incubate the plate at room temperature for 2 hours and then incubate using a suitable cell harvester. Filter the material with a GF / F filter (wet in advance with 0.5% polyethyleneimine). Spend. Rinse filters twice with ice-cold tissue buffer, then remove each filter. Evaluate their radioactivity with a gamma counter. By changing the dilution of the test agent, ¹²⁵I-CRF binding inhibition curves were [P. J. Munson and D. Rodbard, Anal. Biochem. 107: 220 (1980)] to analyze. With this program, the KI value representing inhibition is obtained and their values are used for evaluation of bioactivity. If the KI value representing CRF inhibition is less than about 10,000 nM, the compound is active. is considered sex. Inhibition of CRF-stimulated adenylate cyclase activity Inhibition of CRF-stimulated adenylate cyclase activity was determined by G. Battaglia et al. *Psychopharmacology* 1: 572 (1987). In brief in other words, Tris-HCl (pH 7.4 at 37 ° C.) mM, MgCl₂ 10 mM, EGTA 0.4 mM, 0.1% BSA, isobutylmethylxanthine (IBMX) 1 mM, phosphocreatine kinase 250 mM Unit / ml, creatine phosphate 5 mM, guanosine 5'-triphosphate 100 mM, cCRF 100 nM, antagonist peptide (concentration range 10⁻⁹-10⁻⁶ M) and 0.8 mg of tissue (about 40-60 mg protein) at the original wet weight. The assay is performed in 200 ml of the containing buffer. The reaction was performed with 1 mM ATP / [³²P] ATP (approximately 2-4 mCi / tube), start with 50 mM Tris / 100 ml of HCl, 45 mM ATP and 2% sodium dodecyl sulfate Add and terminate. To monitor cAMP recovery, place each tube before separation. [The³²P] Add 1 µl of [³²P] cAMP (about 40,000 dpm), [³²P] ATP From oil³²The separation of [³²P] cAMP was carried out by eluting sequentially with Dowex and alumina columns. carry out in in vivo bioassay. The in vivo activity of the compounds of the present invention can be measured using bioavailable and accepted biotechnologies in the art. Any of these can be evaluated. Examples of these tests include the sound startle test. Test, stair climb test and chronic administration test. For testing compounds of the present invention. For these and other models useful for W. Berridge and A. J. Dunn, Outlined in *Brain Research Reviews* 15:71 (1990). The compounds could be tested in any rodent or small mammalian species. Compounds of the invention may be used in patients suffering from depression, affective disorders and / or anxiety For imbalance associated with abnormal levels of adrenocorticotrophic hormone-releasing factor Useful for The compound of the present invention is obtained by bringing the active ingredient into contact with the active ingredient action site of the mammalian body. Can be administered to treat these disorders in any manner. These compounds Should be used in combination with individual therapeutic agents or combinations of therapeutic agents Administration can be by any conventional method, as long as it is available. These compounds can be administered alone, but will generally be selected by the chosen route of administration and standard it is administered with a pharmaceutical carrier selected on the basis of pharmaceutical practice. The dosage depends on the method of use and the pharmacodynamic properties of the individual drug, its mode of administration and And route of administration, age, weight and health of recipient, nature and severity of symptoms, combination therapy And the number of treatments, desired effect, and other known factors. The disease or is a compound of the present invention containing 0.002 active ingredients per day for use in the treatment of symptoms. It can also be administered orally at a dose of ~ 200 mg / kg body weight. Desired pharmacological effect To obtain a fruit, it is usually 0.01 to 4 divided doses per day or in a sustained release formulation. -10 mg / kg body weight is effective. Formulations (compositions) suitable for administration may contain from about 1 mg to about 100 mg of active ingredient per unit. It contains. Usually, these pharmaceutical compositions contain about by weight relative to the total weight of the composition. 0.5% to 95% of the active ingredient is present. The active ingredient can be in solid form such as capsules, tablets and powders or Or a liquid such as a syrup and / or suspension. Of the present invention The compounds can also be administered parenterally in sterile solutions. Active ingredients and, but not limited to, lactose, starch, Suitable carriers such as magnesium arate, stearic acid or cellulose derivatives Gelatin capsules can also be used to include Making compressed tablets. Similar diluents can be used for this purpose. Holds both tablets and capsules Can be manufactured as a continuous drug and release the drug continuously over a period of time It is possible to do. Compressed tablets are sugar-coated or film coated and may cause discomfort Masks the taste, protects the active ingredient from the air, or tablets in the gastrointestinal tract Can be selectively disintegrated. Colors and flavors are included in the liquid for oral administration to make it easier for patients to accept. It can also be done. Generally, water, pharmaceutically acceptable oils, saline, dextrose (glucose A) aqueous solutions and related sugar solutions and propylene glycol or polyethylene Glycols, such as len glycol, are suitable carriers for parenteral administration solutions. Non The solution for oral administration contains a water-soluble salt of the active ingredient, suitable stabilizers, and if necessary, a buffer. Preferably, it contains a substance, Sodium bisulfite, sodium sulfite or Antioxidants such as ascorbic acid, alone or in combination, are suitable stabilizers. It is. Also used are citric acid and its salts, and EDTA. In addition, Oral solutions may contain benzalkonium chloride, methylparaben or propylparaben. And preservatives such as chlorobutanol. For suitable pharmaceutical carriers, see Remington, a standard reference in the art. Pharmaceutical Sciences, A. See Osof. Pharmaceutical dosage forms useful for administration of the compounds of the present invention can be described as follows. Capsule Multiple unit capsules are each powdered into standard two-piece hard gelatin capsules Active ingredient 100mg, lactose 150mg, cellulose 50mg and steer Prepared by filling with 6 mg of magnesium phosphate. Soft gelatin capsule Prepare a mixture of the active ingredient with a digestible oil such as soybean oil, cottonseed oil or olive oil. Soft gel containing 100 mg of the active ingredient injected into gelatin with a positive displacement pump A tin capsule was formed. The capsule was washed and dried. Tablet Numerous tablets are prepared in conventional manner, the dosage unit being 100 mg of active ingredient, Silicon dioxide 0.2 mg, magnesium stearate 5 mg, microcrystalline cellulose 275 mg, starch 11 mg and lactose 98.8 mg. Appropriate A good coating can be applied to enhance palatability or slow absorption. The compounds of the present invention are useful for biochemical studies of neurological functions, neurological abnormalities and neurological disorders. It can also be used as a reagent or standard drug in Although the invention has been described and illustrated with respect to certain preferred embodiments, other embodiments have been described. Embodiments will be apparent to those skilled in the art. The present invention is therefore described and illustrated. The present invention is not limited to the specific embodiments that have been described, and should not deviate from the spirit of the present invention. Changes or modifications may be made, the full scope of which is set forth in the following claims. It is.

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(Reference) A61P 3/04 A61P 3/04 3/08 3/08 9/00 9/00 15/00 15/00 15 / 08 15/08 25/08 25/08 25/22 25/22 25/24 25/24 25/28 25/28 25/30 25/30 29/00 29/00 31/18 31/18 37/04 37/04 37/06 37/06 43/00 43/00 111 111 C07D 487/04 142 C07D 487/04 142 145 145 146 146 (31) Priority claim number 03 / 599,242 (32) Priority date Heisei 9 July 23, 1997 (July 23, 1997) (33) Priority Claimed States United States (US) (81) Designated States EP (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), EA (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), A, AU, AZ, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, VN (72) inventor Dorbat, Robert, John, United States 19382 West Chester Kiraeni Lane 1193 Pennsylvania

Patent Citations (7)

Publication number	Priority date	Publication date	Assignee	Title
Family To Family Citations				
US3995339A *	1975-05-27	1976-11-30	Merck & Co., Inc.	Pyrazolo [1,5-a] [1,3,5] triazines
JP56157587A *	1984-08-29	1986-03-24	Shionogi & Co Ltd	Condensed heterocyclic derivative and antiulcerative
US4824834A *	1986-10-31	1989-04-25	Otsuka Pharmaceutical Company, Limited	Pyrazolotriazine compounds
JP2591317B2 *	1989-08-25	1997-12-17	株式会社大塚製薬工場	4-Hydroxy-8- (3-lower alkoxy-4-phenylsulfinylphenyl) pyrazolo [1,5-a] -1,3,5-

				triazine optically active salts and process for producing the same
AU639615B2 *	1990-10-09	1993-07-29	Otsuka Pharmaceutical Co., Ltd.	Pyrimidine derivative, production thereof, and androgen inhibitor
DE69130683T2 *	1991-04-22	1999-05-06	Otsuka Pharma Co Ltd	PYRAZOLO [1,5-a] PYRIMIDINE DERIVATIVES AND ANTI-INFLAMMATORY CONTAINERS THEREOF
US5956897A *	1991-09-09	1994-10-18	Fujisawa Pharmaceutical Co., Ltd.	3-(heteroaryl)-pyrazolo[1,5-a]pyrimidines

* Cited by examiner, † Cited by third party

Cited By (7)

Publication number	Priority date	Publication date	Assignee	Title
WO2004110454A1 *	2003-06-13	2004-12-23	Ishihara Sangyo Kaisha, Ltd.	COMPOSITION FOR TREATMENT FOR OR PREVENTION OF DISEASE NECESSITATING ADMINISTRATION OF ADENOSINE A2a RECEPTOR AGONIST
JP2007567446A *	2003-10-03	2007-03-29	エフ・ホフマン・ラ ロシュ アーゲー	Pyrazolo and imidazo-pyrimidine derivatives
JP2008517067A *	2004-10-19	2008-05-22	エスビー・ファルム コ・ブエルト・リコ・インコーポレイテッド	Pyrazolo [1,5-alpha] pyrimidinyi derivatives useful as corticotropin releasing factor (CRF) receptor antagonists
JP2010504344A *	2006-09-20	2010-02-12	イーライ リリー アンド カンパニ ...	Thiazolopyrazolopyrimidines as CRF1 receptor antagonists
Family To Family Citations				
DE60218434T2 *	2001-03-13	2007-11-08	Bristol-Myers Squibb Pharma Co.	4-(2-BUTYLAMINO)-2,7-DIMETHYL-8-(2-METHYL-6-METHOXYPYRIDE-3-YL) PYRAZOLO-1,5-A8-1,3,5-TRIAZINE, ITS ENANTIOMERIC AND PHARMACEUTICALLY ACCEPTABLE SALTS AS CORTICOTROPIN RELEASING FACTOR RECEPTOR LIGANDS
CN103694242B *	2013-12-10	2016-01-06	昆明赛美科技有限公司	Pyrazolopyrimidines and pharmaceutical composition thereof and its application in pharmacy
CN112479956A *	2019-07-30	2021-03-12	杭州阿诺生物医药科技有限公司	Method for preparing adenosine receptor inhibitor intermediate

* Cited by examiner, † Cited by third party, ‡ Family to family citation

Similar Documents

Publication	Publication Date	Title
US6191131B1	2001-02-20	Azolo triazines and pyrimidines
US6060478A	2000-05-09	Azolo triazines and pyrimidines
KP100548853B1	2006-02-02	Azolo Triazines and Pyrimidines
US6124289A	2000-09-26	Azolo triazines and pyrimidines
JP42283282	2009-02-25	Azolotriazines and azolopyrimidines
US6960683B2	2005-11-01	Pyrazolotriazines as CRF antagonists
US6953341B2	2005-10-25	Pyrazolopyrimidines as CRF antagonists
US6313124B1	2001-11-06	Tetrazine bicyclic compounds
EP1140929B1	2003-10-15	1h-imidazo 4,5-dipyridazin-7-ones, 3h-imidazo 4,5-dipyridin-4-ones and corresponding thiones as corticotropin releasing factor (crf) receptor ligands
JP41945982	2008-12-10	Azolotriazines and Azolopyrimidines
US6754185B2	2004-08-11	Pyrazolo[3,4-d]pyrimidines as corticotropin releasing factor (CRF) antagonists
US7678793B2	2010-03-16	Azolo triazines and pyrimidines
US2003006885A1	2003-01-09	Azolo triazines and pyrimidines
AU2002300983B2	2005-06-09	Azolo Triazines And Pyrimidines

CA2532925C	2009-10-20	Azolo triazines and pyrimidines
AU20023502A	2002-05-02	Azolo triazines and pyrimidines

Priority And Related Applications

Child Applications (1)

Application	Priority date	Filing date	Relation	Title
JP2004216483A	1996-07-24	2004-07-23	Division	Azolotriazines and Azolopyrimidines

Applications Claiming Priority (7)

Application	Filing date	Title
US68604796A	1996-07-24	
US2029096P	1996-07-24	
US08/686,047	1996-07-24	
US60/023,290	1996-07-24	
US08/899,242	1997-07-23	Azolo triazines and pyrimidines
US08/899,242	1997-07-23	
PCT/US1997/013072	1997-07-23	Azolo triazines and pyrimidines

Legal Events

Date	Code	Title	Description
2004-08-12	A521	Written amendment	Free format text: JAPANESE INTERMEDIATE CODE: A523 Effective date: 20040723
2004-08-12	A621	Written request for application examination	Free format text: JAPANESE INTERMEDIATE CODE: A621 Effective date: 20040723
2005-04-26	A711	Notification of change in applicant	Free format text: JAPANESE INTERMEDIATE CODE: A712 Effective date: 20050411
2005-05-19	A521	Written amendment	Free format text: JAPANESE INTERMEDIATE CODE: A523 Effective date: 20050420
2008-05-07	A131	Notification of reasons for refusal	Free format text: JAPANESE INTERMEDIATE CODE: A131 Effective date: 20080507
2008-08-26	A521	Written amendment	Free format text: JAPANESE INTERMEDIATE CODE: A523 Effective date: 20080807
2009-02-17	A02	Decision of refusal	Free format text: JAPANESE INTERMEDIATE CODE: A02 Effective date: 20090217
2009-05-16	A521	Written amendment	Free format text: JAPANESE INTERMEDIATE CODE: A523 Effective date: 20090515
2009-05-29	RD13	Notification of appointment of power of sub attorney	Free format text: JAPANESE INTERMEDIATE CODE: A7433 Effective date: 20090519
2009-06-09	A521	Written amendment	Free format text: JAPANESE INTERMEDIATE CODE: A521

Effective date: 20090519

2009-06-24	A911	Transfer of reconsideration by examiner before appeal (zenchi)	Free format text: JAPANESE INTERMEDIATE CODE: A911 Effective date: 20090625
2009-09-08	A912	Removal of reconsideration by examiner before appeal (zenchi)	Free format text: JAPANESE INTERMEDIATE CODE: A912 Effective date: 20090908
2010-05-12	R013	Notification of appointment of power of sub attorney	Free format text: JAPANESE INTERMEDIATE CODE: A7433 Effective date: 20100511
2010-05-27	A521	Written amendment	Free format text: JAPANESE INTERMEDIATE CODE: A521 Effective date: 20100511
2011-03-17	A61	First payment of annual fees (during grant procedure)	Free format text: JAPANESE INTERMEDIATE CODE: A61 Effective date: 20110319
2014-03-11	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2015-03-19	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2016-03-08	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2017-03-18	LAPS	Cancellation because of no payment of annual fees	

Concepts



machine-extracted

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Name	Image	Sections	Count	Query match
N1C=NC=C2N=CC=C21		title,description	3	0.000
N1N=NC=C2N=CC=C21		title,description	2	0.000
disease		claims,abstract,description	60	0.000
Anxiety		claims,abstract,description	23	0.000
Anxiety disease		claims,abstract,description	23	0.000
anxiety		claims,abstract,description	23	0.000
antagonistic		claims,abstract,description	18	0.000
heart disease		claims,abstract,description	13	0.000
Cardiovascular Disease		claims,abstract,description	7	0.000
compounds		claims,description	691	0.000
fura Nil		claims,description	213	0.000
mixture		claims,description	145	0.000
heteroaryl group		claims,description	140	0.000
sodium chloride		claims,description	133	0.000
aryl group		claims,description	132	0.000
salts		claims,description	131	0.000
heterocyclic group		claims,description	119	0.000
prodrug		claims,description	107	0.000
prodrugs		claims,description	107	0.000
halogen group		claims,description	104	0.000

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bleeding	claims	2	0.000

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⌘ Neurological disorder	abstract,description	6	0.000
⌘ antagonist	abstract,description	6	0.000
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⌘ Corticotropin-Releasing Hormone	abstract,description	4	0.000
⌘ Psychiatric disease	abstract,description	4	0.000
⌘ Irritability	abstract,description	2	0.000
⌘ Corticotropin-Releasing Hormone	abstract	2	0.000
Show all concepts from the description section			

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(74) Agents: **HOSTETTLER, Danica** et al.; Eli Lilly and Company, Patent Division, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

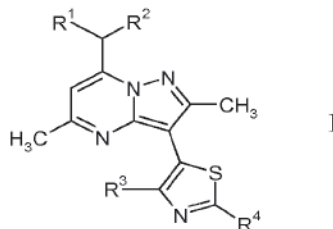
Declarations under Rule 4.17:

- 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
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(54) Title: THIAZOLE PYRAZOLOPYRIMIDINES AS CRF1 RECEPTOR ANTAGONISTS



(57) Abstract: The present invention relates to compounds of Formula (I), pharmaceutical compositions thereof, and use thereof as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndrome.

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THIAZOLE PYRAZOLOPYRIMIDINES AS CRF1 RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to novel thiazole pyrazolopyrimidine compounds,
5 pharmaceutical compositions thereof, and use thereof as CRF1 receptor antagonists in the treatment of psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndrome.

BACKGROUND OF THE INVENTION

10 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
15 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.

CRF has been implicated in psychiatric disorders and neurological diseases
20 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, Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric
25 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.

CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain thereby suggesting potential functional diversity. For
30 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. A more discrete

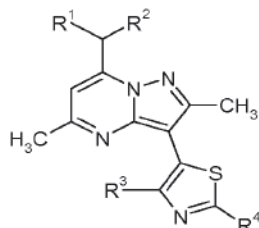
septal/hypothalamic distribution and the availability of alternative endogenous ligands suggest a different functional role for the CRF2 receptor. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF1 receptors is reported to suppress appetite without producing the profile of behavioral activation
 5 observed with selective CRF1 agonism. In other cases, CRF2 agonism produces similar effects to those reported for CRF1 antagonists or CRF1 gene deletion. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well.

Certain pyrrolo[2,3-*d*]pyrimidines, pyrrolo[3,2-*d*]pyrimidines, pyrazolo[1,5-*a*]pyrimidines, 1,2,3-triazolo[4,5-*b*]pyridines, and pyrazolo[1,5-*a*]-1,3,5-triazines, useful
 10 as CRF antagonists, are described in WO 94/13676, WO 97/29109, WO 98/08847, and WO 98/03510.

The present invention provides novel thiazole pyrazolopyrimidines useful as CRF1 receptor antagonists. In view of the above, it is desirable to discover new
 15 efficacious and selective antagonists of CRF1 as potentially valuable therapeutic agents for the treatment of psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndrome. Further, since a majority of commercial CNS and cardiovascular drugs exhibit unfavorable bioavailability and pharmacokinetic profiles, it is also desirable to discover new compounds with favorable bioavailability and pharmacokinetic profiles
 20 relative to known CRF antagonists such as CP154526 and NBI30775.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a compound of Formula I



Formula I

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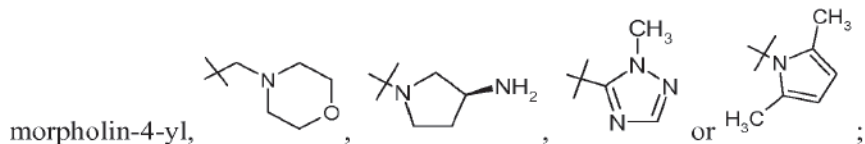
wherein:

R^1 and R^2 are independently ethyl or *n*-propyl;

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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,



R^a and R^b are independently hydrogen, C_1 - C_3 alkyl, $H_2NCH_2CH_2-$,

5 $(CH_3)_3COC(O)NHCH_2CH_2-$, or $CH_3CH_2CH_2NHCH_2CH_2-$;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a pharmaceutical composition comprising: a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another embodiment, the present invention relates to a method of treating depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergy, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulceration, inflammatory disorders, pituitary or ectopic pituitary-derived tumors, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis in a patient, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention relates to use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergy, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulceration, inflammatory disorders, pituitary or ectopic pituitary-derived tumors, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis.

In another embodiment, the present invention relates to a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of depression,

anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergy, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulceration, inflammatory disorders, 5 pituitary or ectopic pituitary-derived tumors, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis.

In another embodiment, the present invention relates to a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in therapy.

10 DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Alkyl" means a saturated aliphatic hydrocarbon group, which may be straight or branched, having 1 to 5 carbon atoms in the chain.

15 "Pharmaceutically acceptable excipient" refers to a pharmaceutically acceptable formulation carrier, solution, or additive to enhance the formulation characteristics. Such excipients must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof and are well known to the skilled artisan (see e.g. *Remingtons Pharmaceutical Sciences*, 19th Edition, Mack Publishing Company, 1995).

20 "Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and 25 isolating the salt thus formed (see e.g. *Remingtons Pharmaceutical Sciences*, 19th Edition, Mack Publishing Company, 1995).

"Therapeutically effective amount" or "effective amount" means the amount of the compound of formula I of the present invention or pharmaceutical composition containing a compound of formula I of the present invention that will elicit the biological 30 or medical response of or desired therapeutic effect on a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The terms "treatment," "treat," "treating," and the like, are meant to include both slowing and reversing the progression of a disorder. These terms also include alleviating, ameliorating, attenuating, eliminating, or reducing one or more symptoms of a disorder or condition, even if the disorder or condition is not actually eliminated and even if

5 progression of the disorder or condition is not itself slowed or reversed. The term "treatment" and like terms also include preventive (e.g., prophylactic) and palliative treatment. Prevention of the disease is manifested by a prolonging or delaying of the onset of the symptoms of the disease.

The symbol "—" in a molecular structure indicates the position of attachment

10 for that particular substituent.

When any variable occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. In choosing compounds of the present

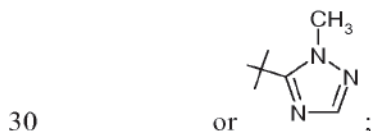
15 invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R^1 , R^2 , etc., are to be chosen in conformity with well-known principles of chemical structure connectivity.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality

20 toward the point of attachment. For example, an arylcarbonylaminoalkyl substituent is equivalent to aryl-C(O)-NH-alkyl-.

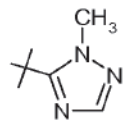
The present invention contemplates the following embodiments, which can alternatively be further combined:

- (a) A compound of Formula I wherein R^1 and R^2 are ethyl;
- 25 (b) A compound of Formula I wherein R^1 and R^2 are *n*-propyl;
- (c) A compound of Formula I wherein R^3 is Cl, Br, methyl or trifluoromethyl;
- (d) A compound of Formula I wherein R^3 is Cl;
- (e) A compound of Formula I wherein R^3 is Br;
- (f) A compound of Formula I wherein R^4 is R^aR^bN -, pyridin-4-yl, morpholin-4-yl,



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(g) A compound of Formula I wherein R⁴ is morpholin-4-yl;



(h) A compound of Formula I wherein R⁴ is

(i) A compound of Formula I wherein R^a and R^b are independently C₁-C₃alkyl;

(j) A compound of Formula I wherein R¹ and R² are ethyl, R³ is Cl, and R⁴ is morpholin-4-yl;

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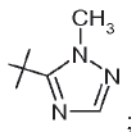
(k) A compound of Formula I wherein R¹ and R² are *n*-propyl, R³ is Cl, and R⁴ is morpholin-4-yl;

(l) A compound of Formula I wherein R¹ and R² are ethyl, R³ is Br, and R⁴ is morpholin-4-yl;

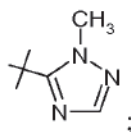
10

(m) A compound of Formula I wherein R¹ and R² are *n*-propyl, R³ is Br, and R⁴ is morpholin-4-yl;

(n) A compound of Formula I wherein R¹ and R² are ethyl, R³ is Cl, and R⁴ is

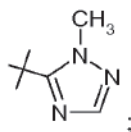


(o) A compound of Formula I wherein R¹ and R² are *n*-propyl, R³ is Cl, and R⁴ is

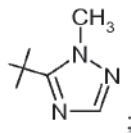


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(p) A compound of Formula I wherein R¹ and R² are ethyl, R³ is Br, and R⁴ is



(q) A compound of Formula I wherein R¹ and R² are *n*-propyl, R³ is Br, and R⁴ is



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(r) Use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for treating depression or anxiety;

- (s) Use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for treating alcohol or substance abuse;
- (t) Use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for treating alcohol or substance abuse and associated withdrawal symptoms;
- 5 (u) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF1 binding of ≤ 500 nM;
- (v) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF1 binding of ≤ 50 nM;
- 10 (w) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF1 binding of ≤ 5 nM;
- (x) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF1 binding of ≤ 500 nM and selectively binding to CRF1 (i.e., lower K_i) relative to CRF2;
- (y) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF1 binding of ≤ 50 nM and selectively binding to CRF1 (i.e., lower K_i) relative to CRF2;
- 15 (z) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a K_i value for CRF1 binding of ≤ 5 nM and selectively binding to CRF1 (i.e., lower K_i) relative to CRF2; and/or
- 20 (aa) Particular exemplified compounds with superior bioavailability and pharmacokinetic profiles relative to some known CRF antagonists (e.g., CP154526 and NBI30775), such as Example 15.

The compounds of the present invention are preferably formulated as
 25 pharmaceutical compositions administered by a variety of routes. Preferably, such compositions are for oral administration. Such pharmaceutical compositions and processes for preparing same are well known in the art (see, e.g., *Remington: The Science and Practice of Pharmacy*, A. Gennaro, et al., eds., 19th ed., Mack Publishing Co., 1995).

30 The compounds of Formula I are generally effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.0001 to about 30

mg/kg of body weight. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, and therefore the above dosage range is not intended to limit the scope of the invention in any way. It will be understood that
5 the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

The compounds of Formula I are CRF-1 antagonists and, as such, are useful for
10 treating a condition which is treatable by reducing CRF1 receptor tone or stimulation. Corticotropin releasing factor (CRF), a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Natl. Acad. Sci (USA)* 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)], has been linked to a number of medical
15 conditions. For example, 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 [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 in the immune system to physiological, psychological, and immunological stressors [see, e.g., J. E. Blalock, *Physiological Reviews* 69:1 (1989); J. E. Morley, *Life Sci.* 41:527 (1987)].

25 CRF is involved in psychiatric disorders and neurological diseases including depression and anxiety [D. M. Nielsen, *Life Sci.* 78:909-919; H. E. Kunzel et al., *J. Psychiatr. Res.* 37:525-533; D. R. Gehlert et al., *Eur. J. Pharmacol.* 509:145-153]. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral
30 sclerosis, as they relate to the dysfunction of CRF neurons in the central nervous system [for a review, see: E. B. De Souza, *Hosp. Practice* 23:59 (1988)]. Chronic administration of CRF has been shown to produce impairment of the dopamine system suggesting a role

in Parkinson's disease [E. Izzo et al., *Pharmacol. Biochem. Behav.* 81:701-708 (2005)]. Other neurological disorders in which CRF is involved include epilepsy [T. Z. Baram et al., *Brain Res.* 770:89-95 (1997)] and migraine [T. C. Theoharides et al., *Endocrinology* 136:5745-5750 (1995)]. CRF has been implicated in alcohol and substance abuse and

5 associated withdrawal symptoms [D. H. Overstreet et al., *Pharmacol. Biochem. Behav.* 77:405-413; Y. Shaham et al., *Psychopharmacology (Berl)* 137:184-190]. Moreover, there is evidence that CRF has a role in various endocrine disorders and cardiovascular diseases such as obesity [E. Timofeeva and D. Richard, *Neuroendocrinology* 66:327-340 (1997)], metabolic syndrome [A. M. Ward et al., *Metabolism* 53:720-726(2004)],

10 congenital adrenal hyperplasia [D. P. Merke and G. B. Cutler Jr., *Endocrinol. Metab. Clin. North Am.* 30:121-135 (2001)], Cushing's disease [M. Labeur et al., *Curr. Drug Targets Immune Endocr. Metabol. Disord.* 4:335-342 (2004)], hypertension [R. J. Briscoe, et al., *Brain Res.* 881:204-207 (2000)], and stroke [S. L. Stevens et al., *J. Cereb. Blood Flow Metab.* 23:1151-1159 (2003)]. Gastric disturbances such as irritable bowel

15 syndrome [Y. Tache et al., *Eur J. Surg. Suppl*:16-22 (2002)] and stress-induced gastric ulceration [K. E. Gabry et al., *Mol. Psychiatry* 7:474-483, 433 (2002)] have been shown to be related to CRF. In addition, there is indication that CRF has a role in various areas of human female health, for example, premenstrual syndrome [F. Facchinetti et al., *Psychosom. Med.* 56:418-422 (1994)], infertility [L. Ghizzoni et al., *Endocrinology*

20 138:4806-4811 (1997)], sexual dysfunction [J. E. Jones et al., *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 283:R591-597 (2002)], and premature labor [P. D. Wadhwa et al., *Am. J. Obstet. Gynecol.* 191:1063-1069 (2004)]. There is also evidence that CRF has a significant role in the immune system indicating therapeutic potential for treating inflammatory disorders [A. Gravanis and A. N. Margioris, *Curr. Med. Chem.* 12:1503-

25 1512 (2005)], allergies [L. K. Singh et al., *Brain Behav. Immun.* 13:225-239 (1999)], multiple sclerosis and other autoimmune disorders [C. Benou et al., *J. Immunol.* 174:5407-5413 (2005)]. In addition to the preceding, CRF has been implicated in visceral pain [M. Nijssen et al., *Neurogastroenterol. Motil.* 17:423-432 (2005)], sleep disorders [T. M. Buckley and A. F. Schatzberg, *J. Clin. Endocrinol. Metab.* 90:3106-

30 3114(2005)], pituitary tumors or ectopic pituitary-derived tumors [K. D. Dieterich et al., *J. Clin. Endocrinol. Metab.* 83:3327-3331 (1998)], chronic fatigue syndrome and

fibromyalgia [G. Neeck and L. J. Crofford, *Rheum. Dis. Clin. North Am.* 26:989-1002 (2000)].

CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain [D. T. Chalmers et al., *TIPS* 17:166-72 (1996)] thereby
5 suggesting potential functional diversity [S. C. Heinrichs et al., *Regul. Peptides* 71:15 (1997)]. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors [G. Liebsch et al., *Regul. Peptides* 59: 229-39 (1995); D. W. Schulz, *PNAS* 93: 10477-82 (1996)]. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors [Heinrichs
10 et al., 1997]. A more discrete septal/hypothalamic distribution [D. T. Chalmers et al., *J. Neurosci.* 15(10): 6340-50 (1995)] and the availability of alternative endogenous ligands [J. Vaughan et al., *Nature* 378: 287-92 (1995)] suggest a different functional role for the CRF2 receptor [Heinrichs et al., 1997]. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF1 receptors is reported to suppress
15 appetite without producing the profile of behavioral activation observed with selective CRF1 agonism (H. Tezval et al., *PNAS* 101(25): 9468-9473 (2004)). In some cases, CRF2 agonism produces similar effects to those reported for CRF1 antagonists or CRF1 gene deletion [S. C. Heinrichs, *Trends in Pharmacological Sciences* 20(8):311-5 (1999)]. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF1
20 antagonists may be an important treatment for obesity as well [C. Contoreggi et al., *Neuroendocrinology* 80(2):111-23 (2004)].

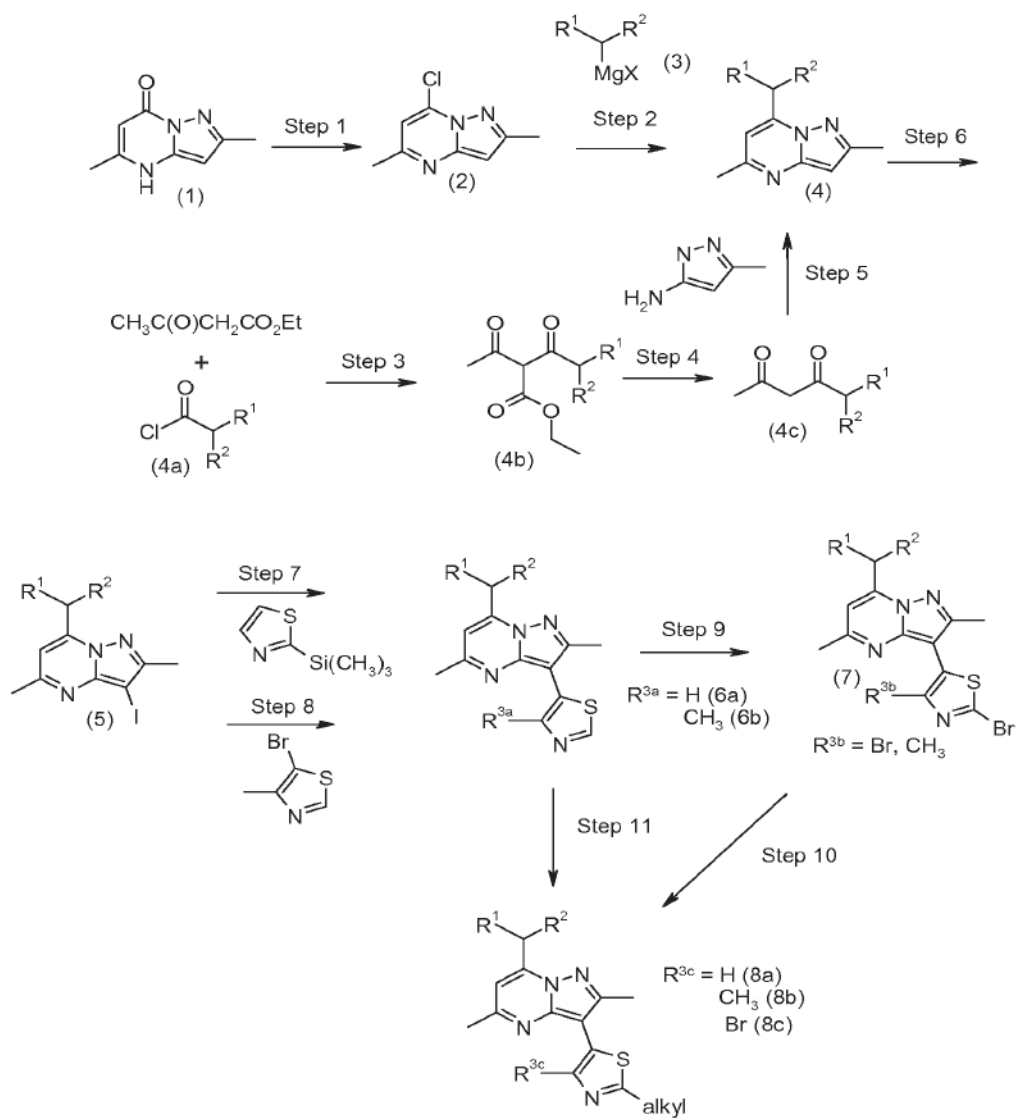
PREPARING COMPOUNDS OF THE INVENTION

All of the compounds of the present invention can be chemically prepared, for
25 example, by following the synthetic routes set forth below. However, the following discussion is not intended to be limiting to the scope of the present invention in any way. For example, the specific synthetic steps for each of the routes described may be combined in different ways, or in conjunction with steps from different schemes, to prepare additional compounds of Formula I. The products of each step can be recovered
30 by conventional methods including extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallization, and the like. In the Schemes below

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all substituents, unless otherwise indicated, are as previously defined and suitable reagents are well known and appreciated in the art.

Scheme 1



5

Formation of a compound of formula (6a,b), (7), or 8(a-c) can be carried out in accordance with reactions as depicted in Scheme 1. An appropriate compound of formula

(6a,b), (7), or (8a-c) is one in which R^1 and R^2 are as defined for formula I and $R^{3a} = H$ or CH_3 , $R^{3b} = Br$ or CH_3 and $R^{3c} = H$, CH_3 , or Br .

In Scheme 1, Step 1, the pyrazolo[1,5-a]pyrimidine-7-one of formula (1) is converted to 7-chloro-2,5-dimethyl- pyrazolo[1,5-a]pyrimidine using phosphorous
5 oxychloride and dimethylaniline in an inert solvent, such as toluene, at the reflux temperature of the solvent.

In Step 2, a Grignard reagent of formula (3) ($X = Cl$ or Br) is reacted with the chloride of formula (2), in an inert solvent such as toluene, at reflux temperature to provide the 7-alkyl pyrazolopyrimidine of formula (4).

10 Alternatively, a 7-alkyl pyrazolopyrimidine of formula (4) can be obtained as shown in Steps 3, 4, and 5. In Step 3 ethyl acetoacetate is acylated with an acid halide of formula (4a) in the presence of magnesium chloride to provide a diketo-ester of formula (4b). The diketo-ester of formula (4b) is decarboxylated under Krapcho conditions to provide the diketone of formula (4c). For example, (4b) is heated in dimethyl sulfoxide at
15 a temperature of about 130 to 170 °C to perform the decarboxylation. In Step 5, the diketone of formula (4c) is cyclized with 3-amino-5-methylpyrazole to give the 7-alkyl pyrazolopyrimidine of formula (4) in a protic solvent such as methanol, ethanol, or acetic acid. Preferred conditions use acetic acid at a temperature of about 0 to 60 °C.

The pyrazolopyrimidine of formula (4) is functionalized to an iodo
20 pyrazolopyrimidine of formula (5) in Step 6 using an excess of N-iodosuccinimide in acetonitrile.

In Scheme 1, Step 7 or 8, the iodo pyrazolopyrimidine of formula (5) is reacted with a thiazole zinc halide in a Negishi cross-coupling reaction to provide a thiazolyl
pyrazolopyrimidine of formula (6a) or (6b) (Jensen, J.; Skjaerback, N.; Vedso, P.
25 *Synthesis* 2001, 128). The thiazole zinc halide is generated using methods well known to those skilled in the art. For example, in Step 7, 2-trimethylsilanylthiazole is treated with *n*-, *sec*-, or *tert*-butyl lithium, followed by lithium-zinc exchange with $ZnCl_2$. The organozinc reagent is coupled with the iodo pyrazolopyrimidine of formula (5) in the presence of a palladium catalyst, for example, dichloro[1,1'-bis(diphenyl-
30 phosphino)ferrocene]palladium (II) dichloromethane, in an inert solvent, such as THF, at reflux temperature for about 12 to 36 hours, to provide a thiazole pyrazolopyrimidine of formula (6a).

Alternatively, in Step 8, a thiazole zinc bromide is generated using 5-bromo-4-methylthiazole and zinc metal, and used in the Negishi cross-coupling essentially as described for Step 7, to provide a thiazole pyrazolopyrimidine of formula (6b).

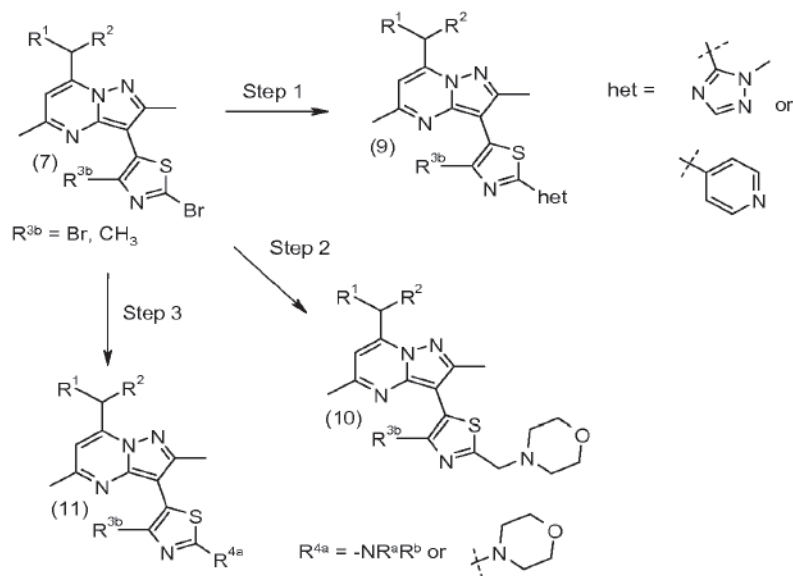
In Scheme 1, Step 9, a thiazole of formula (6a,b) is brominated to give a bromo or
5 dibromo thiazole of formula (7), wherein $R^{3b} = \text{Br}$ or CH_3 . The thiazole is brominated with either 1 or 2 eq of N-bromosuccinimide, depending on whether R^{3a} is CH_3 or H, respectively.

An alkyl thiazole of formula (8a-c) is obtained from either a thiazole of formula (6a,b) in Step 11, or from a bromothiazole of formula (7) in Step 10. In Step 10, halogen-
10 lithium exchange with *n*-, *sec*-, or *t*-butyl lithium provides a thiazole lithium reagent, which is subsequently reacted with electrophiles, such as alkylhalides, like iodomethyl methylether or iodobutane. In Step 11, the thiazole lithium reagent is formed via deprotonation using *n*-, *sec*-, or *tert*-butyl lithium and then subsequently reacted with an electrophile, like iodomethyl methylether or iodobutane.

15 It will be appreciated by one skilled in the art that the thiazole ring system is readily functionalized and that thiazole intermediates such as 2-trimethylsilyl-thiazole (Dondoni, A.; et. al. *J. Org. Chem.* 1988, 53, 1748) can be readily prepared. 5-Bromo-4-methylthiazole is obtained by bromination of 4-methylthiazole with bromine in acetic acid (Collins, I. J., et. al. WO2003093252, 13 Nov 2003). 2,5-Dimethyl-4H-
20 pyrazolo[1,5-a]pyrimidine-7-one (1) is readily prepared by condensation of ethyl acetoacetate and 5-methyl-2H-pyrazol-3-ylamine in refluxing acetic acid.

Scheme 2

14



Formation of a compound of formula (9), (10), or (11) can be carried out in accordance with reactions as depicted in Scheme 2. An appropriate compound of formula (9), (10), or (11) is one in which R¹, R², R^a, and R^b are as defined for formula I and R^{3b} = Br or CH₃, and R^{4a} = -NR^aR^b or -N-morpholinyl and "het" is defined as depicted.

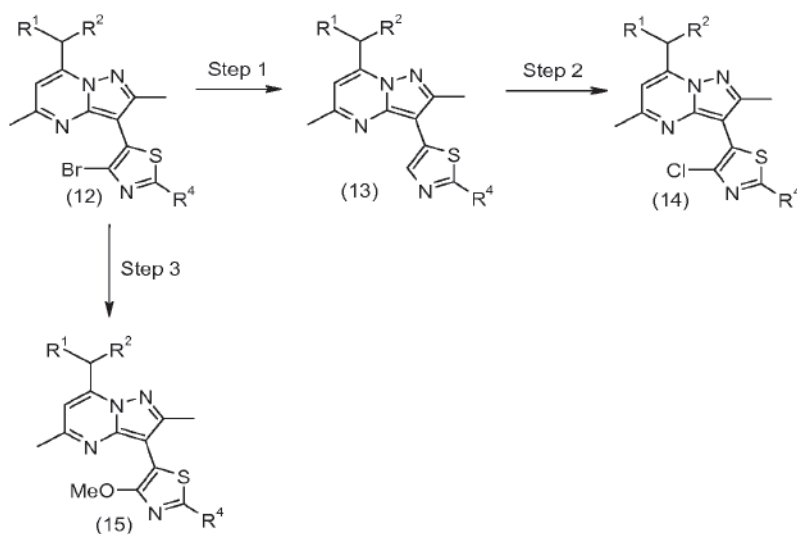
In Step 1, a bromothiazole of formula (7) is coupled with a heterocyclic zinc reagent in a Negishi cross-coupling reaction to provide a thiazole heterocycle of formula (9). For example, 1-methyl-1,2,4-triazole is treated with *n*-, *sec*-, or *tert*-butyl lithium, followed by zinc chloride, at about -80 to -65 °C, and reacted *in situ* with a bromothiazole of formula (7). The reaction is performed preferentially in an inert solvent, such as THF, in the presence of a palladium catalyst, such as dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane or tetrakis(triphenylphosphine)palladium (0). The reaction is warmed to reflux temperature. Alternatively, the heterocyclic zinc reagent is formed from a haloheterocycle, such as 4-iodopyridine and zinc metal.

In Scheme 2, Step 2, an intermediate 2-formyl thiazole is formed via halogen-lithium exchange using *n*-, *sec*-, or *t*-butyl lithium followed by reaction with N-formyl morpholine. The formyl thiazole is subjected to a reductive amination in the presence of an organic amine, such as morpholine, to provide a morpholinyl methyl thiazole of formula (10). Reductive aminations are well-known in the art typically using an

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inorganic borohydride reagent such as sodium borohydride or sodium cyanoborohydride. Preferred conditions use sodium triacetoxyborohydride in an inert solvent such as dichloromethane or THF.

In Step 3, a bromothiazole of formula (7) undergoes a displacement reaction with an amine of formula $\text{--NR}^a\text{R}^b$ or with morpholine to provide an aminothiazole of formula (11). The reaction is preformed in an inert solvent, such as THF or dioxane, using an inorganic base, such as cesium carbonate at 70 to 110 °C.

Scheme 3

10

Formation of a compound of formula (13), (14), or (15) can be carried out in accordance with reactions as depicted in Scheme 3. An appropriate compound of formula (13), (14), or (15) is one in which R^1 , R^2 , and R^4 are as defined for formula I.

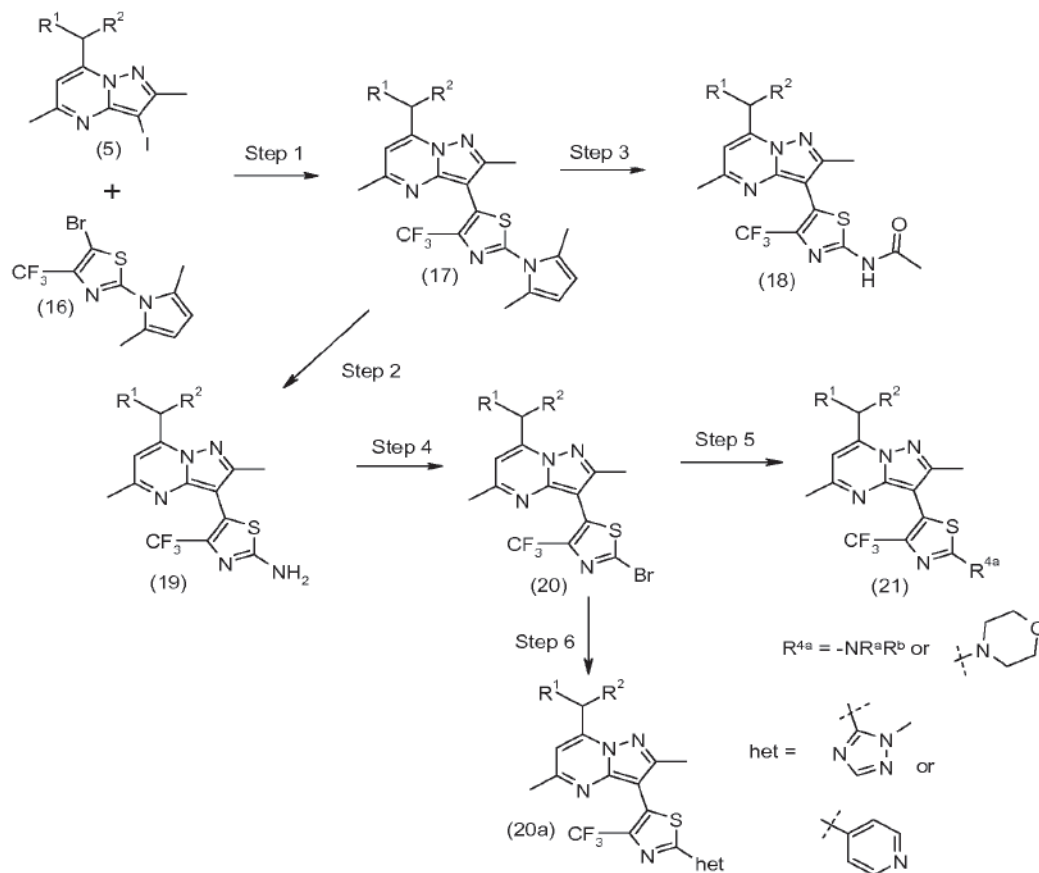
It will be recognized by one skilled in the art that a 4-bromothiazole, such as that of formula (12) is readily manipulated to other functionality. For example, in Step 1, the bromide can be dehalogenated with cuprous chloride to give a thiazole of formula (13) which is subsequently chlorinated with N-chlorosuccinimide to provide a 4-chlorothiazole of formula (14).

In Scheme 3, Step 3, a 4-bromothiazole of formula (12) is displaced with sodium methoxide in the presence of copper (I) iodide in methanol at about 100 to 120 °C in an

16

inert solvent such as dimethylformamide, to provide a 4-methoxy thiazole of formula (15).

Scheme 4



5

Formation of a compound of formula (17), (18), (19), (20), (20a), or (21) can be carried out in accordance with reactions as depicted in Scheme 4. An appropriate compound of formula (17), (18), (19), (20), (20a), or (21) is one in which R^1 , R^2 , R^a , and R^b are as defined for formula I and R^{4a} is $-NR^aR^b$ or $-N$ -morpholinyl and "het" is defined as depicted.

10

In Scheme 4, Step 1, an iodopyrazolopyrimidine of formula (5) and a 5-bromothiazole of formula (16) undergo a Negishi cross-coupling to form a dimethylpyrrolylthiazole of formula (17). For example, the 5-bromothiazole of formula

(16) is treated with *n*-, *sec*-, or *tert*-butyl lithium and then with zinc chloride at about -80 to -65 °C. The organozinc reagent is reacted *in situ* with an iodopyrazolopyrimidine of formula (5). The coupling reaction is performed preferentially in an inert solvent, such as THF, at reflux temperature, in the presence of a palladium catalyst, such as bis(tri-
5 butylphosphine)palladium (0).

In Step 2, a dimethylpyrrolylthiazole of formula (17) is deprotected to provide an aminothiazole of formula (19). The dimethylpyrrole is treated with hydroxylamine in acetic acid at a temperature of about 60 to 100 °C, for about 4 to 8 h, preferably for about 6 h. In Step 3, to form the thiazole acetamide of formula (18), the same conditions are
10 used as in Step 2, with the exception that the reaction is continued for about 72 h.

In Scheme 4, Step 4, a 2-aminothiazole of formula (19) is converted to a 2-bromothiazole of formula (20) using a modified Sandmeyer reaction. Preferred conditions use an alkyl nitrite, such as *t*-butyl nitrite, and copper (II) bromide, in acetonitrile at a temperature of about 60 to 80 °C.

15 In Step 5, a 2-bromothiazole of formula (20) undergoes a displacement reaction with an amine of formula $-NR^aR^b$ or with morpholine to provide an aminothiazole of formula (21). The reaction is performed in an inert solvent, such as methanol, THF, or dioxane, or is treated neat, with an excess of the amine at a temperature of about 70 to 110 °C. Alternatively the reaction is performed with the reacting amine and an excess of
20 triethylamine, or an inorganic base, such as cesium carbonate. Also contemplated in the synthesis of aminothiazoles of formula (21) are various deprotection steps, such as removal of a *tert*-butyl ester carbamic acid (BOC), as may be required or beneficial for carrying out the reactions above wherein $-NR^aR^b$ carries additional amine functionality as defined for formula I. The selection and use of suitable protecting groups is well known
25 and appreciated in the art (see for example, *Protecting Groups in Organic Synthesis*, Theodora Greene (Wiley-Interscience)).

In Scheme 4, Step 6, a 2-bromothiazole of formula (20) is coupled with a heterocyclic zinc reagent in a Negishi cross-coupling reaction to provide a thiazole heterocycle of formula (20a) in a manner similar to that as described for Scheme 2, Step
30 1.

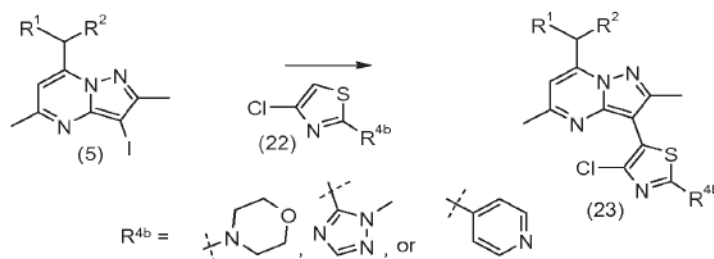
It will be appreciated by the skilled artisan that a functionalized thiazole of formula (16) can be prepared by means known in the art. For example, cyclization of

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thiourea with a bromoketone, such as 3-bromo-1,1,1-trifluoropropan-2-one, provides 4-trifluoromethyl-thiazole-2-ylamine. Subsequent bromination and protection of the amine using hexane-2,5-dione provides (16).

5

Scheme 5



Formation of a compound of formula (23) can be carried out in accordance with reactions as depicted in Scheme 5. An appropriate compound of formula (23) is one in which R¹ and R² are as defined for formula I and R^{4b} is defined as depicted.

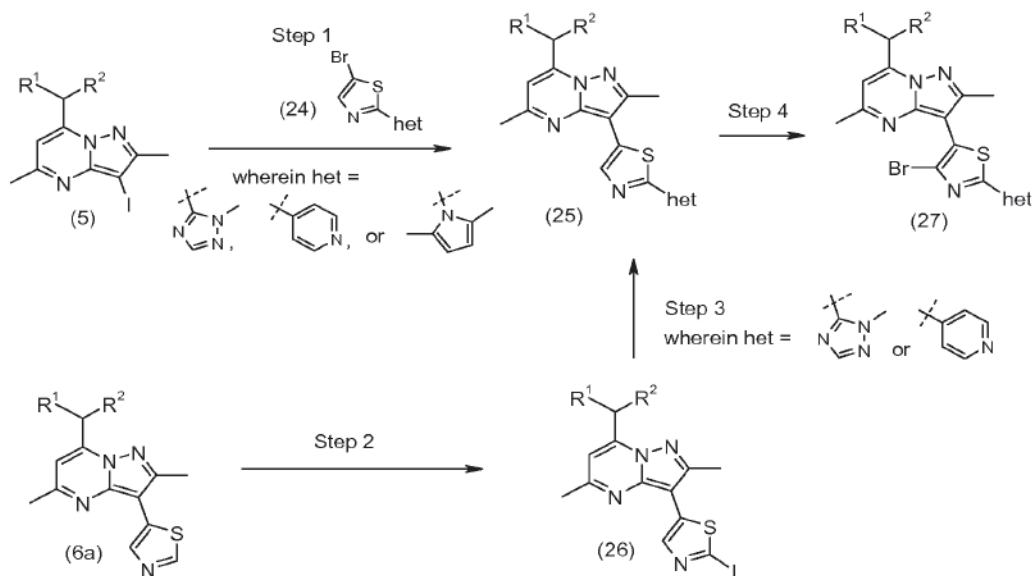
10 An iodopyrazolopyrimidine of formula (5) and a 4-chloro-2-morpholino-thiazole, for example, of formula (22) undergo cross-coupling to form a pyrazolopyrimidine thiazole of formula (23). For example, the reactants are coupled in the presence of copper iodide, palladium acetate, and triphenylphosphine, with a base such as cesium carbonate. The coupling reaction is performed preferentially in an inert solvent, such as DMF, at
15 about 100 – 150 °C for 4 – 24 h.

It will be appreciated by the skilled artisan that a functionalized thiazole of formula (22) can be prepared by means known in the art. For example, 2,4-dichlorothiazole can be reacted with morpholine to give the 2-morpholino-thiazole of formula (22). 2,4-Dichlorothiazole can also be exhaustively brominated to provide 2,5-dibromo-4-chlorothiazole. Subsequent bromine-lithium exchange with *n*-butyl lithium in THF at -90 °C and quench with water provides 2-bromo-4-chlorothiazole [*J. Chem. Soc. Perkin Trans I: Org Bioorg. Chem.* (1972-1999), (2):215-219 (1992)]. 2-Bromo-4-chlorothiazole can be subjected to a Negishi cross-coupling reaction with a heterocyclic zinc reagent to obtain the thiazol-2-yl triazole or pyridine.

25

Scheme 6

19



Formation of a compound of formula (27) can be carried out in accordance with reactions as depicted in Scheme 6. An appropriate compound of formula (27) is one in which R^1 and R^2 are as defined for formula I and "het" is defined as depicted for Step 1 or Step 3, respectively.

In Scheme 6, Step 1, a heterocyclic thiazole, for example, of formula (25) is obtained by reaction of an iodopyrazolopyrimidine of formula (5) with a bromothiazole of formula (24). The reaction is performed in the presence of N-butylammonium bromide and a base, such as potassium acetate with a palladium catalyst such as palladium acetate with tris(2,4-di-*tert*-butyl-phenyl)-phosphane, in an inert solvent such as N-methylpyrrolidinone at a temperature of about 100 – 150 °C.

Alternatively, in Step 2, a thiazolyl pyrazolopyrimidine of formula (6a) is iodinated to provide a 2-iodothiazole of formula (26). The thiazole is treated with lithium diisopropylamide at a temperature of -70 to -80 °C for about one hour and then treated with N-iodosuccinimide at about the same temperature in an inert solvent, such as THF. This is followed by Step 3, wherein a triazolyl or 4-pyridyl thiazole of formula (25) is formed using Negishi cross-coupling conditions similar to those described for Scheme 2, Step 1.

In Scheme 6, Step 4, a thiazolyl pyrazolopyrimidine of formula (25) is brominated to give a bromothiazole of formula (27). The bromination is effected using N-

bromosuccinimide in the presence of a small amount of acetic acid in an inert solvent, such as acetonitrile.

A compound of formula (27), wherein het = 2,5-dimethyl-pyrrol-1-yl, can be further elaborated to obtain compounds of the invention as described in Scheme 4, Steps 2, 3, 4, and 5.

It will be appreciated by the skilled artisan that heterocycle thiazoles of formula (24) can be readily prepared by means known in the art. For example, thiazole-2-carboxylic acid amide can be cyclized to the triazole with 1,1-dimethoxy-N,N-dimethyl-methanamine, followed by N-methyl-hydrazine to obtain the triazolyl thiazole, which can be subsequently brominated with N-bromosuccinimide. Literature procedures afford 4-thiazol-2-yl-pyridine which can be brominated to provide 4-(5-bromo-thiazol-2-yl)-pyridine. 5-Bromo-2-(2,5-dimethyl-pyrrol-1-yl)-thiazole can be readily obtained by reaction of 2-amino-5-bromothiazole with hexane-2,5-dione.

As used herein, "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "LC/MS" refers to liquid chromatography/mass spectrometry; "GC/MS" refers to gas chromatography/mass spectrometry; "HR-ToF" refers to high resolution time-of-flight; "APCI" refers to atmospheric pressure chemical ionization; "δ" refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "EtOAc" refers to ethyl acetate; "MeOH" refers to methanol; "EtOH" refers to ethanol; "DMF" refers to dimethylformamide.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following preparations and examples are provided to describe the invention in further detail. They are intended to illustrate and not to limit the invention in any way whatsoever. The reagents and starting materials are readily available to, or may be readily synthesized by, one of ordinary skill in the art. Examples 1- 35 provide representative compounds and illustrate the preparation thereof. Examples A-D illustrates various biological assays that can be used for determining the biological properties of the compounds of the inventions. Those skilled in the art will promptly recognize appropriate variations from the procedures described in the examples. The names of the compounds of the present

invention are provided by ChemDraw Ultra® version 7.0.1. Salts are named as the free base plus the conjugate acid.

Preparation 1

5 2,5-Dimethyl-4H-pyrazolo[1,5-*a*]pyrimidin-7-one

Add ethyl acetoacetate (128 g, 0.98 mol) dropwise to an acetic acid solution (500 mL) of 5-methyl-2H-pyrazol-3-ylamine (100 g, 0.95 mol), keeping the temperature at 25-28 °C. Heat the mixture at reflux for 10 h and then cool to room temperature. Add the reaction to *tert*-butyl methyl ether (5 L) cooled to 5 °C, keeping the temperature below 10 °C. Stir for 1 h at 5 °C, and filter. Dry the resulting material *in vacuo* overnight to provide a white solid (158 g, 96%).

Preparation 2

7-Chloro-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

15 To a suspension of 2,5-dimethyl-4H-pyrazolo[1,5-*a*]pyrimidin-7-one (10.0 g, 61.3 mmol) in toluene (150 mL) add *N,N*-dimethylaniline (9.7 mL, 76.7 mmol). Add phosphorus oxychloride (11.2 mL, 122.6 mmol) dropwise to this white suspension. Reflux for 3 h under an inert atmosphere, cool to room temperature, and concentrate the reaction to a brown oil using reduced pressure. Dissolve the oil in ethyl acetate (250 mL) and basify with 1.0 N NaOH. Separate the organic phase and extract the basic aqueous phase with ethyl acetate (2 × 100 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure to yield a brown solid. Purify the material using flash chromatography, eluting with 80% hexane/20% (30% THF/hexane) to 0% hexane/100% (30% THF/hexane) in a step gradient of 20% increments to provide a light green solid (6.65 g, 59%). ES/MS *m/z* (³⁵Cl) 182.3 (M+1)⁺.

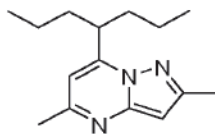
Alternate Procedure:

30 Add 2,5-dimethylpyrazolo[1,5-*a*]pyrimidin-7-one (20 g, 122 mmol) to 1,4-dioxane (60 mL). Stir the mixture at 22 °C for 10 min and then add *N,N*-diethylaniline (20.8 mL, 128 mmol). Stir for an additional 5 min and then add phosphorus oxychloride (11.7 mL, 126 mmol) over 15 min. Stir the mixture at 22 °C for 15 min, then heat to 80-85 °C over 35 min and hold the reaction at this temperature for 1.5 h. Add the cooled reaction mixture slowly to a solution of potassium phosphate dibasic (106.7 g, 612.82

mmol) in water (325 mL) cooled to 0-5 °C, keeping the temperature below 5 °C during the addition. Stir the mixture at 22 °C and then add methyl-*t*-butyl ether (150 mL). Separate the organic layer and extract the aqueous layer with methyl-*t*-butyl ether (2 × 100 mL). Combine the organic portions, dry over sodium sulfate, filter, and evaporate the solvent. Purify by silica gel chromatography, eluting with hexanes/ethyl acetate (2/1) to provide the title compound as a yellow solid (20.7 g, 88%). ES/MS m/z (^{35}Cl) 182 ($M+1$)⁺.

Preparation 3

7-(1-Propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine



Charge an oven dried flask equipped with a reflux condenser, with anhydrous THF (40 mL), iodine (catalytic amount), magnesium ribbon (1.92 g, 78.9 mmol) and 4-bromoheptane (9.4 mL, 52 mmol). Heat the reaction to reflux in an oil bath. The temperature of the reaction spikes as the Grignard reaction is initiated. Stir the reaction an additional 4 h at 90 °C and cool to room temperature. Allow the magnesium metal to settle out (can also be centrifuged) and canulate off the Grignard reagent under positive argon pressure into a flask charged with 7-chloro-2,5-dimethylpyrazolo [1,5-*a*]pyrimidine (4.80 g, 26.3 mmol) in anhydrous toluene (20 mL). Reflux the reaction under an inert atmosphere overnight. Cool the reaction to room temperature and quench with water. Dilute with ethyl acetate (150 mL), then add water (100 mL) and saturated ammonium chloride (50 mL). Separate and extract the aqueous phase with dichloromethane (75 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 80% hexane/20% (20% ethyl acetate/hexane) to 0% hexane/100% (20% ethyl acetate/hexane) in a step gradient of 20% increments to give yellow crystals (3.08 g, 48%). ES/MS m/z 246.3 ($M+1$)⁺.

Alternate Procedure:

- Heat a mixture of magnesium turnings (3.5 g, 144 mmol) and a catalytic amount of iodine (100 mg) in THF (100 mL) to 65 °C under a nitrogen atmosphere. Add a few drops of neat 4-bromoheptane and heat the mixture until the reaction starts. Then add a solution of 4-bromoheptane (17.6 mL, 94.9 mmol) in THF (42 mL) keeping the
- 5 temperature at 65–70 °C over 2 h. Reflux the mixture for an additional hour and then cool the reaction to 22 °C. Add the prepared Grignard reagent to a solution of 7-chloro-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (10.2 g; 53.3 mmol) in THF (60 mL) cooled to 0 °C under a nitrogen atmosphere. Add the magnesium reagent solution via cannula over 45 min while keeping the temperature below 10 °C. Then stir the mixture for an
- 10 additional 30 min at 5 °C. Add to this mixture a 10% aqueous ammonium chloride solution (wt/wt) (125 mL) and stir at 22 °C for 30 min. Separate the organic layer and extract the aqueous layer with ethyl acetate (2 × 25 mL). Combine the organic layers and dry over sodium sulfate. Filter the mixture and evaporate the solvent. Purify the crude material by silica gel flash chromatography using an eluent of hexanes/ethyl acetate (5/1)
- 15 to provide the title compound (8 g, 62%). ES/MS *m/z* 246 (M+1)⁺.

Preparation 3a

7-(1-Propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

Alternate Route

Step 1: 3-Acetyl-3-oxo-4-propyl-heptanoic acid ethyl ester

- 20 Add magnesium chloride (14.63 g, 153.70 mmol) to dichloromethane (500 mL) followed by addition of ethyl acetoacetate (19.55 mL, 20.00 g, 153.79 mmol) all at once and stir at room temperature for one hour. Cool the mixture in an ice water bath and add pyridine (24.86 mL, 24.32 g, 307.39 mmol) dropwise. Add di-*n*-propylacetyl chloride (25.00 g, 153.70 mmoles) dropwise at 0 °C under nitrogen to the white slurry.
- 25 After the addition is complete remove the cooling bath, warm to ambient temperature, and stir for 16 h. Quench the reaction with 1 N HCl (400 mL) and separate the bottom layer. Dry the organic portion over magnesium sulfate, filter, and concentrate under vacuum to give a yellow oil (34 g, 86%). Use the material directly in the next step without further purification.

30 Step 2: 5-Propyl-octane-2,4-dione

Dissolve 3-acetyl-3-oxo-4-propyl-heptanoic acid ethyl ester (32.4 g, 126.39 mmoles) in dimethyl sulfoxide (100 mL) and water (5 mL). Heat the solution at 150 °C

for 6 to 8 h or follow the reaction by GC/MS. Cool the reaction and extract with heptane (3 × 100 mL). Wash the combined organic portions with water (100 mL) and brine (100 mL). Concentrate under vacuum at 50 °C to remove most of the heptane. Obtain 23.29g of an oil and use directly in the next step.

5 **Step 3:** 7-(1-Propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

Mix 5-propyl-octane-2,4-dione (15 g, 81.40 mmol) in acetic acid (15 mL) and cool in an ice bath. Add 5-amino-3-methylpyrazole (7.91 g, 81.40 mmol) portionwise and stir at ambient temperature. Check for completion of the reaction by GC/MS after 3 h. GC indicates correct region isomer in comparison with an authentic sample. Distill off the excess acetic acid. Add water (50 mL) and extract with heptane (50 mL). Wash the heptane with brine (50 mL). Dry the organic layer over MgSO₄, filter, and concentrate under vacuum to give a crude oil (15.8 g, 79%). ¹H NMR (CDCl₃): 6.39 (s, 1H); 6.31 (s, 1H); 3.75 (m, 1H); 2.55 (s, 3H); 2.45 (s, 3H); 1.71 (q, 4H); 1.23 (m, 4H); 0.85 (t, 6H).

15 Prepare the following compound essentially as described in Preparation 3, using either procedure. Use 3-bromopentane to prepare the Grignard reagent.

Prep. No.	Chemical name	Physical data
4	7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidine	ES/MS m/z 218.1 (M+1) ⁺

Preparation 5

7-(1-Propyl-butyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*] pyrimidine

20 Dissolve 7-(1-propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (3.08 g, 12.5 mmol) in anhydrous acetonitrile (25 mL) and add 6 portions (0.70 g each) of N-iodosuccinimide (4.2 g, 18.7 mmol) at 10 minute intervals. Stir over the weekend at room temperature. Strip off the acetonitrile and dilute the oil with dichloromethane (100 mL). Wash with saturated ammonium chloride solution (2 × 50 mL). Collect the organic phase, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure to yield a dark red oil. Purify the oil using flash chromatography, eluting with 100% hexane/0% (20% ethyl acetate/hexane) to 0% hexane/100% (20% ethyl acetate/hexane) in a step gradient of 50% increments to give an orange oil (10.97 g, 87%).

25

¹H NMR (400 MHz, CDCl₃): 6.42 (s, 1H), 3.74-3.70 (m, 1H), 2.58 (s, 3H), 2.46 (s, 3H), 1.74-1.68 (m, 4H), 1.28-1.14 (m, 4H), 0.84 (t, *J* = 7.0 Hz, 6H).

Prepare the compound below essentially as described in Preparation 5.

Prep. No.	Chemical name	Physical data
6	7-(1-Ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5- <i>a</i>] pyrimidine	¹ H NMR (400 MHz, CDCl ₃): 6.44 (s, 1H), 3.59 (m, 1H), 2.61 (s, 3H), 2.49 (s, 3H), 1.86-1.76 (m, 4H), 0.85 (t, <i>J</i> = 7.5 Hz, 6H).

5

Alternate procedure for Preparation 6:

Add acetic acid (1 mL) and N-iodosuccinimide (6.7 g, 29.9 mmol) in one portion to a solution of 7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (6 g, 27.5 mmol) in acetonitrile (60 mL). Stir the mixture at 22 °C for 2 h. Evaporate the solvent and take the residue up in water (50 mL) and methyl-*t*-butyl ether (100 mL). Separate the organic portions, dry over sodium sulfate, filter, and evaporate the solvent to afford the title compound (9.2 g, 96%). ES/MS *m/z* 344 (M+1)⁺.

10

Preparation 7

15

2-Trimethylsilanyl-thiazole

Mix *n*-butyl lithium (20.4 mL, 51.0 mmol, 2.5 M in hexane) with diethyl ether (50 mL) in a three-necked flask, equipped with a dropping funnel and thermometer. Cool to -78 °C and add dropwise a solution of thiazole (4.25 g, 50.0 mmol) in diethyl ether (50 mL). After the addition is complete, stir the reaction mixture at -78 °C for 30 min, followed by addition of chlorotrimethylsilane (5.4 g, 50.0 mmol). Stir at -78 °C for an hour and then warm to room temperature. Quench the reaction by adding saturated sodium bicarbonate. Extract the aqueous layer with diethyl ether. Wash the combined organic portions with brine and dry over sodium sulfate. Filter and concentrate under reduced pressure to give a residue. Purify by distillation to give 8.33 g (52-56 °C/ 15 mm Hg) of title compound. ¹H NMR (400 MHz, CDCl₃) 8.13 (d, 1H, *J*=2.6 Hz), 7.54 (d, 1H, *J* = 2.6 Hz), 0.43 (s, 9H).

25

Preparation 8

5-Bromo-4-methylthiazole

Add bromine (9.27 mL, 182 mmol) to a solution of 4-methylthiazole (15.0 g, 152 mmol) in acetic acid (30 mL) at 0 °C. Slowly warm the reaction mixture to room temperature and stir overnight. Dilute with dichloromethane and wash with 1 N NaOH and brine. Dry the organic layer over sodium sulfate, filter, and concentrate under vacuum. Purify the crude product by silica gel column chromatography, eluting with hexanes/ethyl acetate (5/1) to obtain the title compound (9.94 g, 37%). ¹H NMR (400 MHz, CDCl₃): δ 8.69 (s, 1H), 2.43 (s, 3H).

10

Preparation 9

Thiazole-2-carboxylic acid ethyl ester

To a mixture of 2-trimethylsilylthiazole (135 g, 858.1 mmol) in toluene (1350 mL) add a solution of ethyl chloroformate (98.4 mL, 1.03 mol) in toluene (1350 mL) over 15 min. Stir the reaction at 22 °C for 2 h. Add the solution over aqueous sodium carbonate 25% (wt/wt) (5 L) and stir for 30 min. Separate the organic layer and re-extract the aqueous layer with methylene chloride (2 × 1 L). Combine the organic layers and evaporate the solvent to provide the title compound (134 g, 99%). ES/MS m/z 158 (M+1)⁺.

20

Preparation 10

Thiazole-2-carboxylic acid amide

Add thiazole-2-carboxylic acid ethyl ester (150 g, 0.9 mol) to a mixture of methanol (75 mL) and 30% aqueous ammonium hydroxide (750 mL) and heat the mixture at reflux for 1 h. Then cool to 22 °C and evaporate the methanol under vacuum. Stir the mixture for 30 min at room temperature and filter the solid. Dry the isolated solid under vacuum to afford the title compound (98 g, 85%). ES/MS m/z 129 (M+1)⁺.

Preparation 11

1-Methyl-5-thiazol-2-yl-1H-[1,2,4]triazole

Cool 1,1-dimethoxy-*N,N*-dimethyl-methanamine (240 mL) to 10 °C and add thiazole-2-carboxylic acid amide (60 g, 421 mmol) in three portions. Stir the mixture at

10 °C for 30 min. Then heat the mixture gradually to reflux in 45 min. Distill off the methanol formed and then heat the reaction to 100 °C for 1.5 h. Cool the mixture to 60 °C and remove the excess 1,1-dimethoxy-N,N-dimethyl-methanamine by vacuum distillation. Cool the residue to 22 °C and add hexanes (200 mL). Triturate the mixture
5 for 15 min, filter, and dry the solid to constant weight before using in the next step.

Add the solid isolated above (68 g) to acetic acid (680 mL) and cool the mixture to 10 °C. Add *N*-methyl-hydrazine (27 mL, 509 mmol) at such a rate as to keep the temperature below 15 °C. Warm the mixture to 20 °C in 30 min and then heat gradually to 90 °C. Stir at 90 °C for 30 min and then cool to 22 °C. Remove the acetic acid by
10 vacuum distillation. Add the residue over water and adjust to pH = 8 by adding 25% aqueous sodium hydroxide solution. Extract the aqueous layer with methyl-*t*-butyl ether (3 × 600 mL). Combine the organic layers and evaporate the solvent. Purify the resulting residue by silica gel chromatography using an eluent of hexanes/isopropanol (9/1) to provide the title compound (49 g, 70%). ES/MS *m/z* 167 (M+1)⁺.

15

Preparation 12

5-(5-Bromo-thiazol-2-yl)-1-methyl-1*H*-[1,2,4]triazole

To a mixture of methyl-5-thiazol-2-yl-1*H*-[1,2,4]triazole (6.55 g; 39.4 mmol) and dimethylformamide (32 mL), add *N*-bromosuccinimide (14 g, 78.8 mmol) in three
20 portions over 1 h. Stir the mixture at 22 °C for 18 h and then add to water (300 mL) chilled to 0–5 °C. Separate the aqueous layer and extract with methyl-*t*-butyl ether (2 × 200 mL). Combine the organic layers and wash with 7% aqueous sodium hydrogen carbonate (100 mL) and then dry over sodium sulfate. Filter and evaporate the solvent to afford the title compound (9.5 g, 93%). ES/MS *m/z* (⁷⁹Br/⁸¹Br) 245/247 (M+1)⁺.

25

Preparation 13

2,5-Dimethyl-3-[2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-7-(1-propyl-butyl)-pyrazolo[1,5-*a*]pyrimidine

Combine 5-(5-bromo-thiazol-2-yl)-1-methyl-1*H*-[1,2,4]triazole (6.5 g, 23.8 mmol)
30 and 2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*]pyrimidine (6 g, 24.5 mmol) in *N*-methylpyrrolidinone (58 mL) and stir to complete solution under nitrogen. Then add tetra-*N*-butylammonium bromide (5.47 g, 16.7 mmol) and potassium acetate (11.8 g, 119

mmol) and heat the mixture to 100 °C under a nitrogen atmosphere. Degas the hot mixture by three cycles of vacuum/nitrogen purge. Then add palladium acetate (216 mg, 0.94 mmol) and tris(2,4-di-*tert*-butyl-phenyl)-phosphane (787 mg, 1.2 mmol). Heat the mixture 4 h at 125 °C under nitrogen. Cool the mixture to 22 °C and add to water (750 mL). Extract the aqueous layer with methyl-*t*-butyl ether (3 × 200 mL), combine the organic portions, and evaporate. Purify the residue by filtration through a silica gel pad eluting with hexanes/ethyl acetate (4/1). Combine the product containing fractions and evaporate the solvent to afford the title compound (7 g, 72%). ES/MS *m/z* 410 (M+1)⁺.

10

Preparation 14

2,5-Dimethyl-7-(1-propyl-butyl)-3-thiazol-5-yl-pyrazolo[1,5-*a*] pyrimidine

Charge an oven dried flask with 2-trimethylsilanylthiazole (1.765 g, 11.24 mmol) dissolved in anhydrous THF (30 mL) and chill under an inert atmosphere to -78 °C. Slowly add *n*-butyl lithium (2.5 M hexane solution, 4.5 mL, 11.24 mmol) and stir 30 min at -78 °C. Add anhydrous zinc chloride (2.26 g, 16.58 mmol) in one aliquot and stir 30 min at -78 °C. Allow the reaction to rise to room temperature, stir 30 min, and add 7-(1-propyl-butyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*] pyrimidine (1.624 g, 5.18 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene] palladium (II) dichloromethane (0.423 g, 0.518 mmol). Reflux overnight in an oil bath (90 °C) under an inert atmosphere. Cool the reaction to room temperature, quench with saturated sodium bicarbonate, and dilute with ethyl acetate (150 mL). Separate and extract the aqueous with ethyl acetate (75 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/0% (30% THF/hexane) to 0% hexane/100% (30% THF/hexane) in a step gradient of 10% increments to give a white solid (0.720 g, 42%). ES/MS *m/z* 329.0 (M+1)⁺.

Prepare the compound below essentially as described in Preparation 14.

Prep. No.	Chemical name	Physical data
15	7-(1-Ethyl-propyl)-2,5-dimethyl-3-thiazol-5-yl-pyrazolo[1,5- <i>a</i>]pyrimidine	¹ H NMR (400 MHz, CDCl ₃): δ 8.75 (s, 1H), 8.75 (s, 1H), 8.28 (s, 1H), 6.47 (s, 1H), 3.62-3.55 (m, 1H), 2.65 (s, 3H), 2.61 (s, 3H), 1.89-1.75 (m, 4H), 0.85 (t, 6H, <i>J</i> = 7.5 Hz), 0.85 (t, 6H, <i>J</i> = 7.5 Hz).

Alternate procedure for Preparation 15:

- Add *n*-butyl lithium (76.5 mL, 191 mmol, 2.5 M in hexanes) to a solution of 2-trimethylsilylthiazole (30 g, 191 mmol) in THF (450 mL) at -78 °C under nitrogen,
- 5 keeping the temperature below -74 °C during the addition. Stir the mixture at -78 °C for 30 min and then add zinc chloride, dry powder, (39.9 g, 286 mmol) in one portion and warm the mixture to 22 °C over one hour. Add 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, (30 g, 87 mmol) and 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride (6.5 g, 8 mmol) and heat the mixture to reflux under nitrogen for 8
- 10 h. Cool the mixture to 22 °C and add 10% aqueous ammonium chloride (450 mL). Separate the organic layer and wash the aqueous layer with methyl-*t*-butyl ether (2 × 100 mL). Combine the organic portions, dry over sodium sulfate, filter, and evaporate the solvent to afford the title compound (20.4 g, 78%). ES/MS *m/z* 301 (*M*+1)⁺.

15

Preparation 16

7-(1-Ethyl-propyl)-3-(2-iodo-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

- Add a freshly prepared solution of lithium di-*i*-propylamide (150 mL; 62.4 mmol, 0.6 M in THF) to a mixture of 7-(1-ethyl-propyl)-2,5-dimethyl-3-thiazol-5-yl-pyrazolo[1,5-*a*]pyrimidine, (17.8 g, 62.4 mmol) in THF (100 mL) at -78 °C under a
- 20 nitrogen atmosphere, keeping the temperature below -74 °C during the addition. Stir the mixture at -78 °C for one hour and then add a solution of N-iodosuccinimide (15 g, 63 mmol) in THF (100 mL) keeping temperature below -74 °C. Warm the reaction gradually to 22 °C and then add a 10% aqueous solution of ammonium chloride (300 mL). Separate the organic layer and wash the aqueous layer with methyl-*t*-butyl ether (2
- 25 × 200 mL). Combine the organic layers, dry over sodium sulfate, filter, and evaporate the

solvent. Purify the resulting residue by silica gel chromatography, eluting with hexanes/acetone (5/1) to afford the title compound (15 g, 60%). ES/MS m/z 427 (M+1)⁺.

Example 1

- 5 7-(1-Ethyl-propyl)-2,5-dimethyl-3-(4-methyl-thiazol-5-yl)-pyrazolo[1,5-*a*]pyrimidine
- Add Rieke® zinc (10 g in 100 mL of THF, 13.2 mL, 18.48 mmol) to 5-bromo-4-methylthiazole (2.13 g, 18.48 mmol) and heat at reflux for 2 h. Cool the mixture to room temperature and settle the zinc down by centrifuge. Bubble nitrogen gas through 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (900 mg, 2.62 mmol) in dry
- 10 tetrahydrofuran (10 mL) and add the organozinc bromide solution followed by addition of [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (106 mg, 0.13 mmol). Stir the reaction mixture under reflux overnight and cool to room temperature. Add ammonium chloride solution to the reaction mixture and extract with dichloromethane. Dry the organic portion over sodium sulfate, filter, and remove the solvent under vacuum.
- 15 Purify the crude product by silica gel column chromatography, eluting with hexane/ethyl acetate (3/1) to obtain the title compound (652 mg, 79%). ¹H NMR (400 MHz, CDCl₃): δ 8.80 (s, 1H), 6.48 (s, 1H), 3.63 (m, 1H), 2.57 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, *J* = 7.3 Hz). ES/MS m/z 315 (M+1)⁺.

20

Preparation 17

- 3-(2,4-dibromo-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine
- Dissolve 2,5-dimethyl-7-(1-propyl-butyl)-3-thiazol-5-yl-pyrazolo[1,5-*a*] pyrimidine (3.15 g, 9.59 mmol) in acetonitrile (100 mL) and add N-bromosuccinimide (4.27 g, 24.0 mmol) in one aliquot. Stir overnight under an inert atmosphere and confirm
- 25 the reaction is complete using TLC. Concentrate under reduced pressure, dilute the oil with dichloromethane (150 mL), and wash with water (75 mL). Dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting oil using flash chromatography, eluting with 100% hexane/0% (30% THF/hexane) to 0% hexane/100% (30% THF/hexane) in a step gradient (0-10-15-20-25-
- 30 30-35-40-45-50-100% of 30% THF/hexane) to give yellow crystals (3.70 g, 79%). ES/MS m/z (⁷⁹Br⁸¹Br) 486.7 (M+1)⁺.

Prepare the compounds below essentially as described in Preparation 17, with the exception that dichloromethane is used as the solvent.

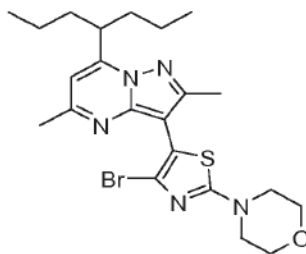
Ex. No.	Chemical name	Physical data
2	3-(2,4-Dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidine	MS (APCI) m/z ($^{79}\text{Br}^{81}\text{Br}$) 459.1 (M+1) ⁺
3*	3-(2-Bromo-4-methyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidine	ES/MS m/z (^{79}Br) 393 (M+1) ⁺

*Use 1.1 eq NBS and stir for 3 days.

5

Example 4

3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine



- Charge an oven dried flask with 3-(2,4-dibromothiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine (0.973 g, 2.00 mmol), anhydrous dioxane (20 mL), morpholine (0.872 g, 10.0 mmol), and cesium carbonate (1.95 g, 6.00 mmol). Reflux in an oil bath (105 °C) under an inert atmosphere overnight. Confirm the reaction is complete using LC/MS. Dilute with ethyl acetate (100 mL), wash with water (50 mL), and back extract the aqueous with ethyl acetate (50 mL). Combine the organic phases, dry over magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/0% (40% dichloromethane/20% ethyl acetate/2% 7 N ammonia in methanol/38% hexane) to 0% hexane/100% (40% dichloromethane/20% ethyl acetate/2% 7 N ammonia in methanol/38% hexane) in a step gradient of 10% increments to yield an off-white solid (0.878 g, 89%). ES/MS m/z (^{79}Br) 491.7 (M+1)⁺.

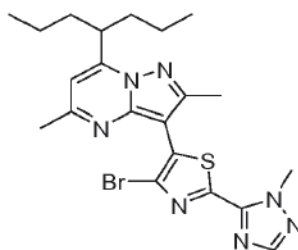
Prepare the following examples essentially as described in Example 4, using as the amine either 2.0 dimethylamine/THF or morpholine, and using THF or dioxane as the solvent. Run reactions in a sealed vessel or Schlenk tube.

Ex. No.	Chemical name	Physical data
5*	{4-Bromo-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5- <i>a</i>] pyrimidin-3-yl]-thiazol-2-yl}-dimethylamine	ES/MS (^{79}Br) 449.8 (M+1) $^{+}$.
6	3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidine	MS (APCI) m/z (^{81}Br) 466.5 (M+1) $^{+}$
7	{4-Bromo-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-thiazol-2-yl}-dimethyl-amine	MS (APCI) m/z (^{81}Br) 424.4 (M+1) $^{+}$
8	{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-4-methyl-thiazol-2-yl}-dimethyl-amine	ES/MS m/z 358 (M+1) $^{+}$
9	7-(1-Ethyl-propyl)-2,5-dimethyl-3-(4-methyl-2-morpholin-4-yl-thiazol-5-yl)-pyrazolo[1,5- <i>a</i>]pyrimidine	ES/MS m/z 400 (M+1) $^{+}$

5 *Use 6 eq of cesium carbonate.

Example 10

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



Charge an oven dried flask with 1-methyl-1,2,4-triazole (0.498, 6.00 mmol) and anhydrous THF (20 mL) and chill under an inert atmosphere to -78 °C. Slowly add *n*-butyl lithium (2.5 M hexane solution, 2.4 mL, 6.0 mmol) and stir 30 min. Add anhydrous zinc chloride (1.36 g, 10.0 mmol) in one aliquot and stir 30 min at -78 °C. Allow the
5 reaction to warm to room temperature, stir 30 min, and add 3-(2,4-dibromothiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine (0.973 g, 2.00 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene] palladium (II) dichloromethane (0.163 g, 0.200 mmol). Reflux the reaction overnight in an oil bath (90 °C) under an inert atmosphere. Cool the reaction to room temperature, quench with water, and dilute with
10 ethyl acetate (100 mL). Separate and extract the aqueous portion with dichloromethane (50 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/0% (10% acetonitrile/40% THF/50% hexane) to 0% hexane/100% (10% acetonitrile/40% THF/50% hexane) in a step gradient of 10%
15 increments to give a white solid (0.090 g, 9%). ES/MS *m/z* (⁷⁹Br) 487.7 (M+1)⁺.

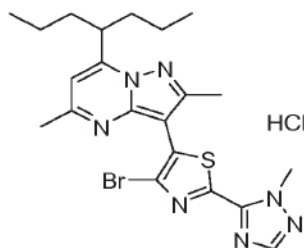
Alternate preparation:

To a solution of 2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-7-(1-propyl-butyl)-pyrazolo[1,5-*a*]pyrimidine (6 g, 14.65 mmol) in acetonitrile (60 mL) add N-bromosuccinimide (2.74 g, 15.4 mmol) in one portion and stir at 22 °C for 10 h.
20 Evaporate the solvent and dissolve the residue in a mixture of water (50 mL) and methyl-*t*-butyl ether (100 mL). Separate the organic layer and extract the aqueous layer with additional methyl-*t*-butyl ether (2 × 50 mL). Combine the organic portions and evaporate the solvent. Purify the resulting material by filtration through a silica gel pad, eluting with hexanes/ethyl acetate (3/1). Combine the product containing fractions and
25 evaporate the solvent. Add heptanes (25 mL) and triturate the solid. Filter the solid and dry under vacuum to afford the title compound (5.5 g, 77%). ES/MS *m/z* (⁷⁹Br/⁸¹Br) 488/490 (M+1)⁺.

Example 10a

3-[4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-
30 butyl)- pyrazolo[1,5-*a*]pyrimidine, hydrochloride

34



- Dissolve 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 (750 mg, 1.54 mmol) in acetone (5 mL) and add 1 M HCl in diethyl ether (1.84 mL, 1.84 mmol). Stir the mixture at room temperature for 3 h and concentrate *in vacuo*. Dissolve the residue in diethyl ether/hexane = 1/1 (5 mL) and crystallize the desired HCl salt (526 mg, 65%). ES/MS m/z (^{81}Br) 490 ($\text{M}+1$)⁺; $^1\text{H-NMR}(\text{CDCl}_3)$: 8.20 (s, 1H), 6.82 (s, 1H), 4.21 (s, 3H), 3.64 (m, 1H), 2.49 (m, 3H), 2.44 (s, 3H), 1.75 (m, 4H), 1.96(m, 4H), 0.81 (m, 6H).

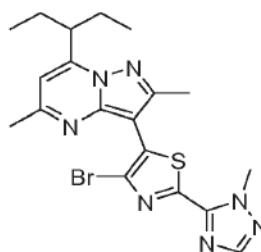
- 10 Prepare the following compound essentially as described in Example 10.

Ex. No.	Chemical name	Physical data
11*	7-(1-Ethyl-propyl)-2,5-dimethyl-3-[4-methyl-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-pyrazolo[1,5-a]pyrimidine	ES/MS m/z 396 ($\text{M}+1$) ⁺

* Use 0.5 M zinc chloride in THF instead of anhydrous zinc chloride. Heat at 80 °C for 3 days.

Example 12

- 15 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



35

Under nitrogen atmosphere, add *n*-butyl lithium (2.5 M in hexane, 0.6 mL, 1.5 mmol) to a solution of 1-methyl-1,2,4-triazole (124.5 mg, 1.5 mmol) in THF (3 mL) at –78 °C and stir for 30 min. Add anhydrous zinc chloride (409 mg, 3.0 mmol), continue stirring for 30 min, warm up to room temperature and stir for 2 h. Add 3-(2,4-dibromothiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (229 mg, 0.5 mmol), followed by tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) and reflux overnight. Cool to room temperature, dilute with ethyl acetate, and wash with saturated ammonia chloride. Dry the organic portion over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with hexanes:ethyl acetate (10:2.5) to give the title compound as a yellow foam (77 mg). MS (APCI) *m/z* (⁷⁹Br) 460.4 (M+1)⁺.

Alternate preparation from Example 21:

Add acetic acid (1 mL) and N-bromosuccinimide (4.1 g, 22 mmol) to a solution of 7-(1-ethyl-propyl)-2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-pyrazolo[1,5-*a*]pyrimidine (8 g, 21 mmol) in acetonitrile (80 mL). Stir the mixture 2 h at 22 °C. Then evaporate the solvent and add water (50 mL) and methyl-*t*-butyl ether (100 mL) to the resulting residue. Separate the organic portion, dry over sodium sulfate, filter, and evaporate the solvent. Recrystallize the resulting residue from isopropyl alcohol to afford the title compound (8.7 g, 90%). ES/MS (*m/z*): (⁷⁹Br/⁸¹Br) 460/462 (M+1)⁺.

20

Example 12a

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, *p*-toluene sulfonic acid

Dissolve 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 (50 mg, 0.109 mmol) in acetone (3 mL). Add a 0.25 M aqueous solution of *p*-toluene sulfonic acid (434.4 μL, 0.109 mmol) and evaporate the resulting mixture to dryness. Add ethyl acetate (12 mL) to get partial dissolution of the solids. Add methanol (1 mL) to achieve a clear solution. Concentrate the solution by slow evaporation until crystals are observed. Isolate the crystals by filtration and dry under vacuum at 25 °C to obtain about 50 mg of the title compound.

30

Determine the stoichiometry of the salt by ion chromatography using the following HPLC conditions: column: Phenomenex Phenosphere SAX, 4.6 × 150 mm at

36

30 °C; mobile phase: 50% acetonitrile/50% 0.025 M sodium phosphate buffer at pH = 4.5; flow rate = 1.5 mL/min; detection: UV at 205 nm; injection volume = 5 µL; run time = 3 min. Theoretical amount calc: 27.2% tosylate; found: 28.4% tosylate (average of three HPLC runs).

5

Example 13

{4-Chloro-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidin-3-yl]-thiazol-2-yl}-dimethylamine

- Charge an oven dried flask with {4-bromo-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidin-3-yl]-thiazol-2-yl}-dimethylamine (0.20, 0.44 mmol) and anhydrous THF (3.0 mL) and chill under an inert atmosphere to -78°C. Slowly add *n*-butyl lithium (1.6 M hexane solution, 0.42 mL, 0.67 mmol) and stir 30 min. Add *N*-chlorosuccinimide (0.120 g, 0.889 mmol) in one aliquot and stir 30 min at -78 °C. Allow the reaction to warm to room temperature, and stir for 5 h, checking the progress using LC/MS. Dilute with ethyl acetate (100 mL), wash with saturated ammonium chloride (50 mL), and back-extract the aqueous with dichloromethane (50 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/0% (25% THF/hexane) to 0% hexane/100% (25% THF/hexane) in a step gradient of 10% increments to give a white solid (0.087 g, 48%). ES/MS *m/z* (³⁵Cl) 406.0 (*M*+1)⁺.

20

Prepare the following examples essentially as described in Example 13 using the appropriate bromothiazole prepared above.

Ex. No.	Chemical name	Physical data
14	3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5- <i>a</i>] pyrimidine	ES/MS <i>m/z</i> (³⁵ Cl) 448.0 (<i>M</i> +1) ⁺
15	{4-Chloro-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-thiazol-2-yl}-dimethyl-amine	MS (APCI) <i>m/z</i> (³⁵ Cl) 378.0 (<i>M</i> +1) ⁺

25

Preparation 18

37

2,4-dichlorothiazole

Cool to 5 °C a mixture of thiazolidine-2,4-dione (50 g, 0.43 mol) in phosphorus oxychloride (240 mL) and add pyridine (34 mL, 0.43 mol) over 15 min. Heat the mixture to 125 °C for 4 h and then cool to 22 °C. Remove the excess phosphorus oxychloride by vacuum distillation and add the residue to water (1 L) chilled to a temperature of 5 °C. Extract the mixture with methylene chloride (3 × 400 mL). Combine the organic portions and evaporate the solvent to afford the title compound (50 g, 76%). EI/MS m/z : ($^{35}\text{Cl}^{35}\text{Cl}/^{35}\text{Cl}^{37}\text{Cl}/^{37}\text{Cl}^{37}\text{Cl}$) 153/155/157 ($M+1$)⁺.

10

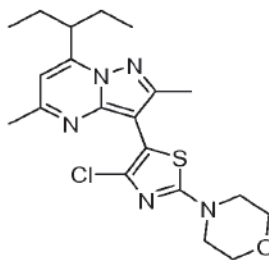
Preparation 19

4-chloro-2-morpholino-thiazole

To a mixture of 2,4-dichlorothiazole (34 g, 0.22 mol) in acetonitrile (425 mL) add potassium carbonate (60.9 g, 0.44 mol) and then morpholine (21.2 mL, 0.225 mol) dropwise over 30 min. Reflux the mixture at 40 °C and then cool to 22 °C. Filter the mixture and evaporate the filtrate. Triturate the residue with *i*-propyl alcohol (60 mL) at 22 °C for one hour. Filter the solids and dry under vacuum to a constant weight to afford the title compound (34.5 g, 76%). ES/MS m/z (^{35}Cl) 205 ($M+1$)⁺.

20

Example 16

3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

Under a nitrogen atmosphere dissolve 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (116 mg, 0.25 mmol) in THF (1.5 mL) and chill to -78 °C. Add *n*-butyl lithium (0.1 mL, 2.5 M in hexane, 0.25 mmol) and stir at -78 °C for 30 min. Add *N*-chlorosuccinimide (33.4 mg, 0.25 mmol) and stir

38

for another 30 min, slowly warming to room temperature. After stirring overnight, quench the reaction by adding a solution of saturated ammonia chloride and extract with ethyl acetate. Wash the organic layer with brine, dry over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with
5 hexanes:dichloromethane:ethyl acetate (5:5:2) to provide the title compound (54 mg). MS (APCI) m/z (^{35}Cl) 420.6 ($\text{M}+1$) $^{+}$; ^1H NMR (400 MHz, CDCl_3): 6.44 (s, 1H), 3.79 (t, 4H, $J=4.8$ Hz), 3.63-3.56 (m, 1H), 3.47 (t, 4H, $J=4.8$ Hz), 2.55 (s, 3H), 2.45 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, 6H, $J=7.5$ Hz).

Alternate Preparation from Preparation 6:

10 Combine 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, (9 g, 26.2 mmol) and 4-chloro-2-morpholino-thiazole (7.5 g, 36.7 mmol) in dimethylformamide (90 mL) previously degassed with nitrogen. Add cesium carbonate (17.8 g, 55 mmol), copper iodide (250 mg, 1.31 mmol), triphenylphosphine (550 mg, 2.09 mmol) and palladium acetate (117 mg, 0.52 mmol). Heat the mixture to 125 °C for 16 h
15 and then cool to 22 °C. Add water (900 mL) and extract with methyl-*t*-butyl ether (3 × 200 mL). Combine the organic portions and evaporate the solvent. Purify by silica gel chromatography eluting with hexanes/ethyl acetate (4/1) to afford the title compound (6.4 g, 62%). ES/MS m/z (^{35}Cl) 420 ($\text{M}+1$) $^{+}$.

20

Example 16a

3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, hydrochloride

25 Dissolve 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (1.40 g, 3.33 mmol) in acetone (10 mL) at 50 °C and cool to room temperature. Add hydrogen chloride (2 M in diethyl ether, 2.0 mL, 4.0 mmol) and stir well in a sonicator. Concentrate the solution a little and add a minimal amount of diethyl ether to crystallize the HCl salt. Cool the mixture in a refrigerator
30 overnight. Add additional hydrogen chloride (2 M in diethyl ether, 2.0 mL, 4.0 mmol) and cool in a refrigerator. Filter the crystalline material and dry to obtain the title compound (1.15 g, 75%). ES/MS m/z (^{35}Cl) 420 ($\text{M}+1$) $^{+}$; ^1H NMR(CDCl_3): 9.18 (br,

1H), 6.86 (s, 1H), 3.72 (m, 4H), 3.49(m, 1H), 3.39 (m, 4H), 2.48 (s, 3H), 2.38(s, 3H), 1.79 (m, 4H), 0.79 (m, 6H).

Example 17

3-(4-Bromo-2-butyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

Under a nitrogen atmosphere, add *n*-butyl lithium (2.5 M in hexane, 0.2 mL, 0.5 mmol) to a solution of 3-(2,4-dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (230 mg, 0.5 mmol) in THF (3 mL) at -78°C . After 30 min, add 1-iodobutane (138 mg, 0.75 mmol) and continue stirring for 1 hour. Warm up to room temperature and stir for one hour. Quench the reaction by adding saturated ammonia chloride solution and extract with ethyl acetate. Dry the organic portion over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with hexanes/ethyl acetate (10/1.5) to give the title compound as orange foam (78 mg). ES/MS m/z (^{81}Br) 437.4 (M+1) $^{+}$.

Prepare the following example essentially as described in Example 17.

Ex. No.	Chemical name	Physical data
18	3-(4-Bromo-2-methoxymethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidine	MS (APCI) m/z (⁸¹ Br) 424.6 (M+1) ⁺

Example 19

20 7-(1-Ethyl-propyl)-3-(2-methoxymethyl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-
a]pyrimidine

Under a nitrogen atmosphere, add *n*-butyl lithium (2.5 M in hexane, 0.4 mL, 1.0 mmol) to a solution of 7-(1-ethyl-propyl)-2,5-dimethyl-3-thiazol-5-yl-pyrazolo[1,5-a]pyrimidine (300 mg, 1.0 mmol) in THF (3 mL) at -78 °C. Stir 30 min and add 1-iodomethyl methyl ether (205 mg, 1.2 mmol). Continue stirring for one hour and then slowly warm up to room temperature and stir overnight. Quench the reaction by adding saturated ammonium chloride solution and extract with ethyl acetate. Wash the organic layer with brine, dry over sodium sulfate, filter, and concentrate under vacuum to a

residue. Purify the crude material by flash chromatography, eluting with hexanes/ethyl acetate (10/2) to give the title compound as a yellow foam (184 mg). MS (APCI) m/z 345.3 (M+1)⁺.

5

Example 20

3-(4-Chloro-2-methoxymethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

Add *n*-butyl lithium (2.5 M in hexanes, 174 mL, 0.43 mmol) to a stirred solution of 7-(1-ethyl-propyl)-3-(2-methoxymethyl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (150 mg, 0.43 mmol) in THF (3 mL) at -78 °C. Stir for 30 min and add *N*-chlorosuccinimide (87 mg, 0.653 mmol). Stir 30 min and then warm the reaction slowly to room temperature allowing the reaction to continue overnight. Quench the reaction by adding saturated ammonium chloride solution, extract with ethyl acetate, dry over sodium sulfate, filter, and concentrate to a residue. Purify by flash chromatography, eluting with hexanes/ethyl acetate (10/2) to give the title compound (7 mg). MS (APCI) m/z (³⁵Cl) 379.3 (M+1)⁺.

20

Example 21

7-(1-Ethyl-propyl)-2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-pyrazolo[1,5-*a*]pyrimidine

Mix 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 (175 mg, 0.38 mmol) and copper(I) chloride (132 mg, 1.33 mmol) in DMF (5 mL) and heat to 120 °C for 24 h. Cool to room temperature, dilute with ethyl acetate, and wash with brine. Dry the organic layer over sodium sulfate, filter, and concentrate under vacuum to a residue. Purify by flash chromatography, eluting with hexanes and then hexanes/EtOAc (10/1.8) to give a yellow-orange solid (45 mg). ES/MS m/z 382.0 (M+1)⁺.

25

Alternate Preparation:

Add *n*-butyl lithium (2.5 M in hexanes, 57.6 mL, 144 mmol) to a solution of *N*-methyltriazole (11.95 g, 144 mmol) in THF (600 mL) at -78 °C under a nitrogen atmosphere, keeping the temperature below -74 °C during the addition. Then add zinc chloride, dry powder, (26 g, 192 mmol) in one portion and warm the mixture to 22 °C in

30

one hour. Add 7-(1-ethyl-propyl)-3-(2-iodo-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (12.5 g, 29 mmol) and tetrakis(triphenyl)phosphine palladium catalyst (1.15 g, 0.01 mol) in one portion and heat the mixture to reflux under nitrogen for 8 h. Cool the mixture to 22 °C and add water (300 mL). Separate the organic layer and extract the aqueous layer with methyl-*t*-butyl ether (2 × 200 mL). Combine the organic portions, dry over sodium sulfate, filter, and evaporate the solvent. Purify by passing over a silica gel pad eluting with hexanes/ethyl acetate (4/1) to afford the title compound (8 g, 72%). ES/MS *m/z* 382 (M+1)⁺.

Example 22

10 3-(4-Chloro-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

Stir a mixture of 7-(1-ethyl-propyl)-2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-pyrazolo[1,5-*a*]pyrimidine (20 mg, 0.052 mmol) and N-chlorosuccinimide (7.6 mg, 0.0569 mmol) in dichloromethane (0.5 mL) and acetonitrile (0.5 mL) at room temperature overnight in a vial. Concentrate to a residue. Purify by flash chromatography, eluting with hexanes and then with hexanes/ethyl acetate (10/1.5) to give the title compound (16 mg). ES/MS *m/z* (³⁵Cl) 416.0 (M+1)⁺.

Example 23

20 7-(1-Ethyl-propyl)-3-(4-methoxy-2-morpholin-4-yl-thiazol-5-yl)- 2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

Stir a mixture of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (162 mg, 0.35 mmol), sodium methoxide (57 mg, 1.05 mmol) and copper(I) iodide (67 mg, 0.35 mmol) in methanol (3 mL) in a sealed 4-mL vial for 15 h at 120 °C. Cool to room temperature, remove the solid by filtration, and concentrate the filtrate under vacuum. Purify the residue by flash chromatography, eluting with hexanes/THF (10/2). Recrystallize the material from methanol to give the title compound (20 mg). ES/MS *m/z* 416.0 (M+1)⁺.

Preparation 20

30 4-Bromo-5-[7-(1-ethyl-propyl)- 2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-thiazole-2-carbaldehyde

- Under a nitrogen atmosphere, add *n*-butyl lithium (1.6 M in hexanes, 0.312 mL, 0.50 mmol) to a THF solution (2.5 mL) of 3-(2,4-dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (230 mg, 0.50 mmol) at -78 °C and stir for 30 min. Add a THF (0.5 mL) solution of N-formyl morpholine (58 mg, 0.50 mmol).
- 5 Stir for one hour, then store the reaction at -20 °C overnight. Warm the reaction to room temperature, dilute with ether, and quench by adding 4 N HCl (4 mL). Separate and extract the organic phase with 4 N HCl (2 × 4 mL). Combine the aqueous portions, treat with solid sodium bicarbonate to pH = 8 to 9 and then extract with diethyl ether. Combine all the organic layers, wash with brine, dry over sodium sulfate, filter, and
- 10 concentrate to a residue. Purify the crude material by flash chromatography, eluting with hexanes/dichloromethane/ethyl acetate (5/5/1) to give the title compound (154 mg). MS (APCI) m/z (^{81}Br) 409.0 (M+1) $^{+}$.

15

Example 24

3-(4-Bromo-2-morpholin-4-yl-methyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

- Combine 4-bromo-5-[7-(1-ethyl-propyl)- 2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-thiazole-2-carbaldehyde (150 mg, 0.368 mmol), morpholine (35 mg, 0.405 mmol) and sodium triacetoxyborohydride (97 mg, 0.46 mmol), in dichloromethane (3 mL) and methanol (0.5 mL). Stir overnight, add additional morpholine (35 mg, 0.405 mmol), and sodium triacetoxyborohydride (97 mg, 0.46 mmol), and stir 4 h more. Remove the solvent under vacuum, dilute with dichloromethane, and wash with brine. Dry the
- 20 organic phase over sodium sulfate, filter, and concentrate under vacuum. Purify the resulting material using flash chromatography, eluting with dichloromethane:2 M ammonia in methanol (10:1) to give a mixture. Purify the mixture using a reverse phase column, eluting with water/acetonitrile (80/20) to water/acetonitrile (10/90) to give the title compound (20 mg). ES/MS m/z (^{81}Br) 480.0 (M+1) $^{+}$.

30

Example 25

3-(4-Bromo-2-pyridin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

Under a nitrogen atmosphere, add *n*-butyl lithium (1.6 M in hexane, 0.312 mL, 0.5 mmol) to a solution of 3-(2,4-dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (229 mg, 0.5 mmol) in THF (4 mL) at -78 °C. After stirring for 30 min, add anhydrous zinc chloride (264 mg, 1.5 mmol) and continue stirring for 30 min. Warm the reaction to room temperature and stir for one hour. Add 4-iodopyridine (103 mg, 0.5 mmol), followed by 1,1'-bis (diphenylphosphino)ferrocene palladium (II) chloride (dichloromethane adduct) (0.408 mg, 0.05 mmol). Heat the reaction to reflux overnight. Cool to room temperature, dilute with ethyl acetate, and wash with water and brine. Dry the organic layer over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with dichloromethane:2 N ammonia in methanol (10:0.75) to give a mixture. Purify the mixture using a reverse phase column, eluting with water:acetonitrile = 80:20 to water: acetonitrile = 10:90, to give the title compound (19 mg). ES/MS m/z (^{79}Br) 456.0 ($M+1$)⁺.

Preparation 21

4-Trifluoromethyl-thiazole-2-ylamine

Add thiourea (4.0 g, 52.3 mmol) and 3-bromo-1,1,1-trifluoropropan-2-one (5.5 mL, 10 g, 52.3 mmol) to ethanol (100 mL) and heat at 50 °C for 2 h. Cool to room temperature and concentrate to dryness. Dissolve the residue in water and adjust the pH to >12 with 2 M NaOH. Extract with diethyl ether (4×). Dry the combined organic extracts with sodium sulfate, filter, and concentrate under vacuum. Purify the resulting material by silica gel chromatography (CH₂Cl₂) to obtain the title compound (6.9 g, 79%). ES/MS m/z 169 ($M+1$)⁺.

Preparation 22

5-Bromo-4-trifluoromethyl-thiazol-2-ylamine, hydrobromide

Add bromine (2.0 mL, 6.28 g, 39.3 mmol) dropwise to an ice-bath cooled solution of 4-trifluoromethyl-thiazole-2-ylamine (6.0 g, 35.7 mmol) in diethyl ether (60 mL). Stir for one hour after the addition is complete and then warm to room temperature. Collect

the solids by filtration and wash with diethyl ether to obtain the title compound (10.5 g, 90%). ES/MS m/z ($^{79}\text{Br}/^{81}\text{Br}$) 247/249 ($M+1$)⁺.

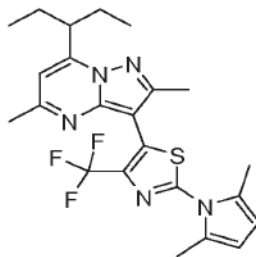
Preparation 23

5 5-Bromo-2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazole

Add hexane-2,5-dione (3.5 mL, 3.4 g, 30.2 mmol) to a solution of 5-bromo-4-trifluoromethyl-thiazol-2-ylamine hydrobromide (9.0 g, 27.4 mmol) in methanol (60 mL). Stir at room temperature overnight. Add phosphate buffer (50 mL, pH = 7). Collect the resulting precipitate by filtration, washing with water. Dissolve the filter cake in CH_2Cl_2 and dry over sodium sulfate. Filter and concentrate under vacuum to obtain the title compound (8.2 g, 92%). ^1H NMR (400 MHz, CDCl_3) δ 5.91 (s, 2H), 2.27 (s, 6H).

Example 26

15 3-[2-(2,5-Dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazol-5-yl]-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine



Cool a solution of 5-bromo-2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazole (2.2 g, 6.6 mmol) in THF (25 mL) in a dry ice bath. Add *t*-butyl lithium (1.7 M in pentane, 8.5 mL, 14.5 mmol) dropwise. Stir for 45 min and then add zinc chloride (0.5 M in THF, 14.6 mL, 7.3 mmol) dropwise. Stir 5 min and remove the cooling bath. Stir 30 min and then add 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (1.5 g, 4.4 mmol) and bis(tri-*t*-butylphosphine)palladium (0) (450 mg, 0.9 mmol). Reflux for 24 h. Cool the reaction, pour the mixture into diethyl ether, and wash with water (2 $\times$). Extract the combined water layers with diethyl ether. Dry the combined organic portions over sodium sulfate, filter, and concentrate to dryness under vacuum. Purify the resulting residue by silica gel chromatography (75-100% CH_2Cl_2 in hexanes) to give the title

45

compound (1.47 g, 72%). HR-ToF-MS m/z calcd for $C_{23}H_{26}F_3N_5S+H^+$: 462.1939, found: 462.1915.

Example 27

5 5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamine

Add hydroxylamine (2 mL, 50% in water) to a solution of 3-[2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazol-5-yl]-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (1.1 g, 2.3 mmol) in acetic acid (10 mL). Heat the reaction to
10 80 °C for 6 h. Cool to room temperature. Pour into diethyl ether and wash with 2 M NaOH (2×) and then once with water. Dry the organic portion over sodium sulfate, filter, and concentrate to dryness under vacuum. Purify the resulting residue by silica gel chromatography (40% ethyl acetate in hexanes) to give the title compound (0.76 g, 87%). ES/MS m/z 384 (M+1)⁺.

15

Preparation 24

3-(2-Bromo-4-trifluoromethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

20 Heat a mixture of copper(II) bromide (540 mg, 2.4 mmol) and *t*-butylnitrite (0.36 mL, 310 mg, 3.0 mmol) in acetonitrile (20 mL) to 60 °C. Add 5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamine (755 mg, 2.0 mmol) as a solid. Heat the reaction to 80 °C for 2 h. Cool the reaction, pour into diethyl ether and extract with water (3×). Dry the organic layer over sodium sulfate,
25 filter, and concentrate to dryness under vacuum. Purify the resulting residue by silica gel chromatography in CH_2Cl_2 to give the title compound (0.77 g, 87%). ES/MS m/z (⁷⁹Br/⁸¹Br) 447, 449 (M+1)⁺.

Example 28

30 {5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine

Heat a sealed tube containing 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (313 mg, 0.7 mmol), and dimethyl amine (2 M in THF, 4 mL, 8 mmol) in methanol (4 mL) to 80 °C for 2 h. Cool the reaction and concentrate under vacuum. Purify the resulting residue by silica gel chromatography, eluting with 0-30% ethyl acetate in CH₂Cl₂, to give the title compound (0.28 g, 97%). HR-ToF-MS *m/z* calcd for C₁₉H₂₄F₃N₅S+H⁺ 412.1770, found: 412.1783.

Prepare the following example essentially as described for Example 28 with the exception that the reaction is refluxed for 8 h.

Ex. No.	Chemical name	Physical data
29	7-(1-Ethyl-propyl)-2,5-dimethyl-3-(2-morpholin-4-yl-4-trifluoromethyl-thiazol-5-yl)-pyrazolo[1,5- <i>a</i>]pyrimidine	HR-ToF-MS <i>m/z</i> calcd for C ₂₁ H ₂₆ F ₃ N ₅ OS+H ⁺ : 454.1873, found: 454.1888

10

Example 30

N-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-acetamide

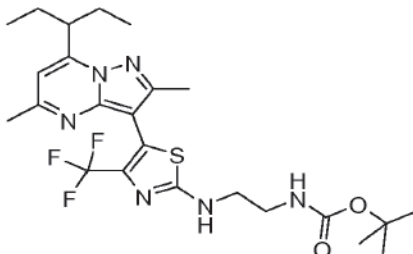
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Add hydroxylamine (50% in water, 5 mL) to a solution of 3-[2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazol-5-yl]-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (2.4 g, 5.2 mmol) in acetic acid (25 mL). Heat the reaction to 80 °C for 72 h. Cool the reaction to room temperature, pour into diethyl ether and wash with 2 M NaOH (2×) and then once with water. Dry the organic portion over sodium sulfate, filter, and concentrate to dryness. Purify the resulting residue by column chromatography, eluting with 40% ethyl acetate in hexanes to give the title compound (0.28 g, 13%). HR-ToF-MS *m/z* calcd for C₁₉H₂₂F₃N₅OS+H⁺ 426.1575, found: 426.1565.

25

Example 31

(2-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamino}-ethyl)-carbamic acid *tert*-butyl ester



- Add (2-amino-ethyl)-carbamic acid *tert*-butyl ester (0.5 mL, 506 mg, 3.2 mmol) to a solution of 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (100 mg, 0.22 mmol) and triethylamine (0.3 mL, 222 mg, 2.2 mmol) in methanol (1 mL). Evaporate off the methanol and heat to 80 °C overnight. Cool the reaction to room temperature and concentrate under vacuum. Purify the resulting residue by column chromatography, eluting with 10-50% ethyl acetate in CH₂Cl₂, to give the title compound (0.11 g, 97%). ES/MS *m/z* 527.2 (M+1)⁺.

Prepare the compounds below as essentially described in Example 31 using the appropriate amine.

Prep. or Ex. No.	Chemical name	Physical data
Prep. 25*	[2-({5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-propyl-amino)-ethyl]-carbamic acid <i>tert</i> -butyl ester	ES/MS <i>m/z</i> 569.3 (M+1) ⁺
Prep. 26**	(S)-(1-{5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-pyrrolidin-3-yl)-carbamic acid <i>tert</i> -butyl ester	ES/MS <i>m/z</i> 553.3 (M+1) ⁺

Ex. 32***	<i>N</i> -{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}- <i>N,N'</i> -dipropyl-ethane-1,2-diamine, hydrochloride	ES/MS <i>m/z</i> 511.2 (<i>M</i> +1) ⁺
------------------	--	---

* Heat at reflux in EtOH overnight. Evaporate EtOH and heat at 110 °C for 24 h.

** Heat at 80 °C in EtOH overnight.

*** Make the HCl salt and recrystallize from EtOAc/hexanes.

5

Example 33

*N*¹-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-ethane-1,2-diamine, hydrochloride

Add (2-{5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamino}-ethyl)-carbamic acid *tert*-butyl ester (101 mg, 0.192 mmol) to 1 M HCl in methanol (1 mL). Heat the reaction at 70 °C overnight. Cool the reaction and concentrate under vacuum from methanol/ethyl acetate. Triturate the resulting residue with ethyl acetate to obtain the title compound (64 mg, 78%). ES/MS *m/z* 427.0 (*M*+1)⁺.

15

Prepare the following examples essentially as described for Example 33.

Ex. No.	Chemical name	Physical data
34	<i>N</i> ¹ -{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}- <i>N</i> ¹ -propyl-ethane-1,2-diamine, hydrochloride	ES/MS <i>m/z</i> 469.2 (<i>M</i> +1) ⁺
35	(<i>S</i>)-1-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5- <i>a</i>]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-pyrrolidin-3-ylamine, hydrochloride	ES/MS <i>m/z</i> 453.0 (<i>M</i> +1) ⁺

Example A

In Vivo Potency Assessment Using Ex Vivo Binding

To assess in vivo potency, a compound of the present invention is evaluated using ex vivo binding. Using the procedures as provided in D. R. Gehlert *et al.*, *EJP* 509: 145-153 (2005), a compound is administered to a rat via the oral route. The binding of ¹²⁵I-

sauvagine to the cerebellum is then assessed ex vivo as described in Gehlert *et al.* For example, Example 15 provides 65% inhibition at 10 mg/kg.

Example B

5 CRF1 Filter Binding Assay

The limitations of plasmid-based human CRF1 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF1 cell line is used to prepare membranes and binding reactions (200 μ L) are set up as follows: 50 μ L of ^{125} I-sauvagine (0.2 nM final), 50 μ L compound and 100 μ L CRF1 membrane (25 μ g/reaction). The reactions are incubated at room temperature for 2 h and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are washed twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM MgCl_2 , 0.05% BSA, pH 7.2), air dried over night and counted with 100 μ L Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 μ M non-labeled sauvagine. Triplicate determinations are typically run and the median data points plotted by Graph Pad Prism.

Using this assay, the exemplified compounds of the present invention inhibit the binding of ^{125} I-Sauvagine (4 nM) in roller/adherent cells with a K_i (inhibition constant) below 1 μ M. For example, Example 15 exhibits a K_i of 6.2 nM.

Example C

CRF2 Filter Binding Assay

The limitations of plasmid-based human CRF2 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF2 cell line is used to prepare membranes and binding reactions (200 μ L) are set up as follows: 50 μ L of ^{125} I-sauvagine (0.2 nM final concentration), 50 μ L compound and 100 μ L CRF2 membrane (25 μ g/reaction). The reactions are incubated at room temperature for 2 hours and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are washed twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM MgCl_2 , 0.05% BSA, pH

7.2), air dried over night and counted with 100 μ L Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 μ M non-labeled sauvagine. Alternatively, compounds are evaluated using a Scintillation Proximity assay. This assay is set up as follows: 50 μ L of ^{125} I-Sauvagine (0.2 nM final concentration), 50
5 μ L compound or non-labelled sauvagine (NSB) and 100 μ L containing 250 μ g wheat germ agglutinin (WGA) SPA beads and CRF2 membrane (1.5 μ g/reaction). Plates are incubated for 4-5 h at room temperature and then centrifuged at 200 X g for 10 min. Bound radioactivity is assessed using a Wallac Trilux scintillation counter. Binding is assessed typically using triplicate determinations and the median data points plotted by
10 Graph Pad Prism. Compounds are initially screened at a fixed concentration and, if sufficient activity is noted, subsequent concentration-response curves are generated.

Particular exemplified compounds of the present invention are tested in the CRF2 binding assay and exhibit weak affinity for the CRF2 receptor. For example, Example 15
15 exhibits 11% inhibition at a concentration of 50 μ M. This result suggests that the compounds of the present invention are selective for the CRF1 receptor, (relative to CRF2).

Example D

Bioavailability and Pharmacokinetic Properties

20 The volume of distribution (Vdist) relates the amount of the drug in the body to the concentration of the drug in the blood or plasma. The volume of distribution refers to the fluid volume that would be required to contain the total amount of the drug in the body at the same concentration as in the blood or plasma: $V_{dist} = \text{amount of drug in the body} / \text{concentration of drug in blood or plasma}$ (Goodman and Gillman's). For a 10 mg
25 dose and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which the drug is present in the extravascular tissue. A large volume of distribution reflects the tendency of a compound to bind to the tissue components compared with plasma protein binding. In a clinical setting, Vdist can be used to determine a loading dose to achieve a steady state
30 concentration.

To test for volume of distribution, Male Sprague Dawley rats (N=3) are administered a single 1 mg/kg intravenous dose of compound. Multiple plasma samples

are collected at time points from 0.08 to 24 hours post-dose. The plasma samples are analyzed by LC/MS/MS to determine the plasma concentrations. Plasma pharmacokinetic calculations are performed to determine the pharmacokinetic parameters including Vdist and plasma clearance (CLp).

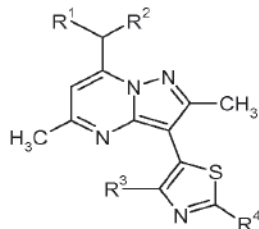
- 5 Compounds of the present invention preferably have favorable bioavailability profiles. For example, a majority of commercial CNS and cardiovascular drugs exhibit a human Vdist of <10 L/Kg. In comparison with CRF antagonists, CP154526 (Schulz et al., *Proc. Natl. Acad. Sci. (USA)*, 93:10477 (1996)) and NBI30775 (Chen et al., *Drug Development Research*, 65:216 (2005)), which exhibit a rat Vdist of 114 L/Kg and 76
10 L/Kg, respectively, when analyzed separately. Example 15 of the present invention, when analyzed separately, exhibits a rat Vdist of only 7.2 L/Kg following a single intravenous dose of 1 mg/kg.

- Further, the plasma clearance (CLp) is a measure of the rate of removal of the drug from the body. Following an intravenous dose and first-order kinetics, the plasma
15 clearance may be determined using the following equation: $CLp = Dose / AUC$, where AUC is the total area under the curve that describes the concentration of the drug in the plasma as a function of time from zero to infinity. Reference CRF antagonists CP154526 and NBI37582 exhibit rat clearance (CLp) of 83 and 306 mL/min/kg, respectively, when
analyzed separately, following a single intravenous dose, while Example 15 of the present
20 invention, when analyzed separately, exhibits a rat CLp of only 23.6 mL/min/kg.

52

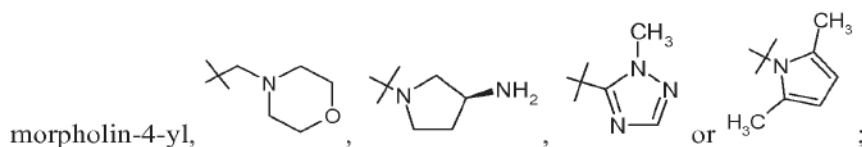
WE CLAIM:

1. A compound of Formula I



Formula I

5 wherein:

 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,

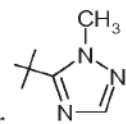
10 R^a and R^b are independently hydrogen, C_1 - C_3 alkyl, $H_2NCH_2CH_2-$, $(CH_3)_3COC(O)NHCH_2CH_2-$, or $CH_3CH_2CH_2NHCH_2CH_2-$;
or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is Cl, Br, methyl or trifluoromethyl.

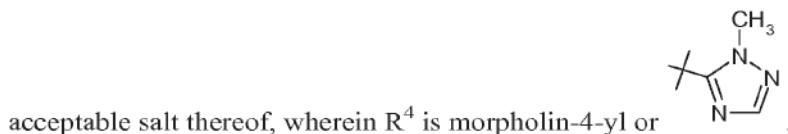
3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^3 is Cl or Br.

20 4. The compound according to any one of claims 1 to 3, or a pharmaceutically

acceptable salt thereof, wherein R^4 is R^aR^bN- , pyridin-4-yl, morpholin-4-yl, or



5. The compound according to any one of claims 1 to 4, or a pharmaceutically



6. The compound according to any one of claims 1 to 4, or a pharmaceutically
5 acceptable salt thereof, wherein R⁴ is R^aR^bN- and R^a and R^b are independently C₁-C₃alkyl.

7. The compound according to claim 1, or a pharmaceutically acceptable salt
thereof, which is 3-[4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-
10 dimethyl-7-(1-propyl-butyl)- pyrazolo[1,5-*a*]pyrimidine.

8. The compound according to claim 1, or a pharmaceutically acceptable salt
thereof, which is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-
15 propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

9. The compound according to claim 1, or a pharmaceutically acceptable salt
thereof, which is 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-
dimethyl-pyrazolo[1,5-*a*]pyrimidine.

- 20 10. A pharmaceutical composition comprising: a compound according to any
one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically
acceptable excipient.

11. A method of treating depression, anxiety, alcohol or substance abuse, obesity,
25 hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep
disorders, allergy, migraine, premenstrual syndrome, infertility, sexual dysfunction,
congenital adrenal hyperplasia, Cushing's disease, premature labor, stress-induced gastric
ulceration, inflammatory disorders, pituitary or ectopic pituitary-derived tumors, chronic
fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis in a patient,
30 comprising: administering to a patient in need thereof a therapeutically effective amount

of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof.

12. A method of treating anxiety or depression in a patient, comprising:
5 administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof.

13. A method of treating alcohol or substance abuse in a patient, comprising:
10 administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof.

14. A compound according to any one of Claims 1 to 9, or a pharmaceutically
15 acceptable salt thereof, for use in therapy.

15. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergy, migraine, premenstrual syndrome, infertility,
20 sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulceration, inflammatory disorders, pituitary or ectopic pituitary-derived tumors, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis.

25
16. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the treatment of anxiety or depression.

17. A compound according to any one of claims 1 to 9, or a pharmaceutically
30 acceptable salt thereof, for use in the treatment of alcohol or substance abuse.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/078605

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/505 A61P29/00 A61P25/22 A61P25/24
A61P25/30

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)
C07D

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, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>GEHLERT ET AL: "3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine: a novel brain-penetrant, orally available corticotropin-releasing factor receptor 1 antagonist with efficacy in animal models of alcoholism." THE JOURNAL OF NEUROSCIENCE, vol. 27, no. 10, 7 March 2007 (2007-03-07), pages 2718-2726, XP002465426 figure 1; table 1</p>	1-17
Y	<p>WO 01/23388 A (NEUROGEN CORP [US]; PFIZER [US]; DARROW JAMES W [US]; LOMBAERT STEPHAN) 5 April 2001 (2001-04-05) page 69; example 95 page 13, line 3</p>	1-17

☒ 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
- *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.
- *&* document member of the same patent family

Date of the actual completion of the international search

22 January 2008

Date of mailing of the international search report

31/01/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gettins, Marc

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/078605

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/072202 A (BRISTOL MYERS SQUIBB PHARMA CO [US]) 19 September 2002 (2002-09-19) claims 1,16	1-17
A	HE LIQI ET AL: "4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-a]-1,3,5-triazine: A Potent, Orally Bioavailable CRF1 Receptor Antagonist" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, 2000, pages 449-456, XP002196777 ISSN: 0022-2623 table 1	1-17
A	WO 2005/063755 A (SB PHARMCO INC [US]; NEUROCRINE BIOSCIENCES INC [US]; LUO ZHIYONG [US]) 14 July 2005 (2005-07-14) claims 1,24	1-17
A	WO 00/59908 A (DU PONT PHARM CO [US]) 12 October 2000 (2000-10-12) page 21, line 15; claims 1,11	1-17
A	WO 97/29109 A (JANSSEN PHARMACEUTICA NV [BE]; NEUROCRINE BIOSCIENCES INC [US]; CHEN C) 14 August 1997 (1997-08-14) cited in the application page 1, line 5 - line 9; claim 1	1-17
Y	WO 98/03510 A (DU PONT MERCK PHARMA [US]) 29 January 1998 (1998-01-29) cited in the application page 162, line 20 - page 164, line 6; claim 1	1-17
Y	CHEN C ET AL: "DESIGN OF 2,5-DIMETHYL-3-(6-DIMETHYL-4-METHYLPYRIDIN-3-YL)-7-DIPROPYL AMINOPYRAZOLO[1,5-ALPHA]PYRIMIDINE (NBI 30775/R121919) AND STRUCTURE-ACTIVITY RELATIONSHIPS OF A SERIES OF POTENT AND ORALLY ACTIVE CORTICOTROPIN-RELEASING FACTOR RECEPTOR ANTAGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 47, no. 19, 9 September 2004 (2004-09-09), pages 4787-4798, XP001206057 ISSN: 0022-2623 figure 1	1-17

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/078605

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:

Although claims 11-13 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 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 allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an 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 reportcovers 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

Information on patent family members

International application No

PCT/US2007/078605

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0123388	A	05-04-2001	AT 347553 T AU 7737900 A BG 106507 A CA 2379633 A1 CN 1377355 A CZ 20021089 A3 DE 60032249 T2 EP 1218381 A2 ES 2277855 T3 HU 0203131 A2 JP 2003510326 T JP 2007077144 A NO 20021357 A OA 12049 A PL 354982 A1 ZA 200202517 A	15-12-2006 30-04-2001 29-12-2002 05-04-2001 30-10-2002 13-11-2002 19-07-2007 03-07-2002 01-08-2007 28-01-2003 18-03-2003 29-03-2007 23-05-2002 02-05-2006 22-03-2004 28-03-2003
WO 02072202	A	19-09-2002	AR 032986 A1 AT 355102 T BG 108189 A BR 0208357 A CA 2440553 A1 CN 1509196 A DE 60218434 T2 DK 1368094 T3 EE 200300435 A EP 1368094 A1 ES 2282401 T3 HK 1057182 A1 HR 20030822 A2 HU 0303480 A2 IS 6947 A JP 2004530662 T MX PA03008185 A NO 20034023 A NZ 528207 A RU 2292347 C2 SK 11572003 A3 TW 257388 B UA 74634 C2 US 2007054913 A1 YU 71503 A ZA 200306995 A	03-12-2003 15-03-2006 30-09-2004 29-06-2004 19-09-2002 30-06-2004 08-11-2007 02-07-2007 15-12-2003 10-12-2003 16-10-2007 06-07-2007 30-04-2004 28-01-2004 10-09-2003 07-10-2004 29-01-2004 11-09-2003 24-02-2006 27-01-2007 03-02-2004 01-07-2006 15-12-2003 08-03-2007 25-05-2006 08-09-2004
WO 2005063755	A	14-07-2005	AR 046967 A1 AU 2004309168 A1 BR PI0417943 A CA 2550948 A1 CN 1938309 A EP 1697374 A1 JP 2007515472 T KR 20070009537 A US 2007287705 A1	04-01-2006 14-07-2005 17-04-2007 14-07-2005 28-03-2007 06-09-2006 14-06-2007 18-01-2007 13-12-2007
WO 0059908	A	12-10-2000	AU 4203500 A	23-10-2000
WO 9729109	A	14-08-1997	AT 336495 T AU 713673 B2	15-09-2006 09-12-1999

Form PCT/ISA/210 (patent family annex) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/078605

Patent document cited in search report	Publication date	Patent family member(s)	Publication date		
WO 9729109	A	AU	1599197 A	28-08-1997	
		BG	102349 A	26-02-1999	
		BR	9707391 A	20-07-1999	
		CN	1205009 A	13-01-1999	
		CZ	9802445 A3	14-10-1998	
		DE	69736513 T2	05-04-2007	
		DE	880523 T1	04-07-2002	
		DK	0880523 T3	26-03-2007	
		EA	980394 A1	29-10-1998	
		EE	9800124 A	15-10-1998	
		EP	0880523 A1	02-12-1998	
		ES	2168237 T1	16-06-2002	
		HU	9900575 A2	28-06-1999	
		ID	15905 A	14-08-1997	
		JP	3356291 B2	16-12-2002	
		JP	2000503661 T	28-03-2000	
		JP	2002121194 A	23-04-2002	
		NO	981357 A	03-08-1998	
		NZ	330119 A	28-02-2000	
		SK	106398 A3	02-12-1998	
		TR	9800792 T2	21-07-1998	
		TW	449599 B	11-08-2001	
WO 9803510	A	29-01-1998	AT	375344 T	15-10-2007
			AU	3894297 A	10-02-1998
			EP	0915880 A1	19-05-1999
			HU	0102187 A2	28-11-2001
			LV	12292 A	20-06-1999
			RO	121272 B1	28-02-2007
			TW	542827 B	21-07-2003
			TW	238164 B	21-08-2005

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2009/058722

International filing date (day/month/year)
29.09.2009

Priority date (day/month/year)
02.10.2008

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Lange, Tim

Telephone No. +31 70 340-2475



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2009/058722

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2009/058722

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-18</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-18</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-18</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1 Reference is made to the following documents:

D1 WO 2008/036579 A1 (LILLY CO ELI [US]; CHEN ZHAOGEN [US];
HAMDOUCHI CHAFIQ HAMDOUCHI [US];) 27 March 2008 (2008-03-27)
cited in the application

Re Item V

Reasoned statement with regard to novelty and inventive step

Novelty

2 The present application **does meet** the criteria of Article 33(1) PCT, because the subject-matter of claims 1-18 **is new** in the sense of Article 33(2) PCT.

2.1 The prior art document D1 discloses: Two processes towards 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(dialkylmethyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine. The first process uses 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(dialkylmethyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine as intermediate (see D1, page 36-37, example 14 & 16), where the 4-Bromo- is exchanged for 4-chloro by lithiation and quenching with NCS. The second process uses 7-(dialkylmethyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine as intermediate, which is coupled to 4-Chloro-2-morpholino-thiazole under Heck reaction conditions (see D1, page 37, example 16/alternate preparation).

2.2 The difference between the present application and the prior art disclosure D1 is that D1 does not describe a process, where the final product is obtained by **reacting a 2,5-dihalogenated thiazol-4-yl-pyrazolo[1,5-a]pyrimidine derivative with morpholine**.

2.3 The claimed intermediate 3-(2,4-dichloro-thiazol-5-yl)-7-(dialkylmethyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine has not been reported in the prior art and therefore is also novel.

2.4 Consequently, **claims 1-18 are novel.**

3 **Inventive step**

3.1 The present application **does meet** the criteria of Article 33(1) PCT, because the subject-matter of claims 1-18 **does involve an inventive step** in the sense of Article 33(3) PCT.

3.2 D1 has been identified as the closest prior art. Document D1 discloses: Two processes towards 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(dialkylmethyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine. The first process uses 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(dialkylmethyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine as intermediate (see D1, page 36-37, example 14 & 16), where the 4-Bromo- is exchanged for 4-chloro by lithiation and quenching with NCS. The second process uses 7-(dialkylmethyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine as intermediate, which is coupled to 4-Chloro-2-morpholino-thiazole under Heck reaction conditions (see D1, page 37, example 16/alternate preparation).

3.3 The difference between the present application and the prior art disclosure D1 is that D1 does not describe a process, where the final product is obtained by **reacting a 2,5-dihalogenated thiazol-4-yl-pyrazolo[1,5-a]pyrimidine derivative with morpholine.**

3.4 The technical effect of this difference is an increased yield in the last step. D1 reports a 48% yield or 62% yield for the last step (see D1, example 16 and 16/alternate preparation), whereas the present application reports a 91% or 89% yield for the last step (see present application, pages 12-13).

3.5 The objective technical problem to be solved, when departing from D1 as the closest prior art can be formulated as: provision of an alternative process towards 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(dialkylmethyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, that is higher yielding in the last step.

3.6 The solution as presented by the applicant is not obvious. A skilled person could not foresee, that the presently claimed process is higher yielding and is therefore a solution to the objective technical problem to be solved.

- 3.7 Consequently, the process of claim 2 is inventive. With the process being inventive, the claimed intermediate, which is the subject-matter of claim 1, is also inventive.
- 3.8 Therefore, the subject matter of the **claims 1-18 are inventive.**

Re Item VIII.

Certain observations on the international application

- 4 The application does not meet the requirements of Article 6 PCT, because claims 10 and 15 are not clear:
- 4.1 Claim 10 has as technical feature that the solvent for the process is "DMAC". This abbreviation is leading to a lack of clarity, as the 4-letter code may be interpreted as "dimethyl acetamide" or "dimethylacetic acid" (see "Gmelin abbreviations of compounds or methods", ISBN 3-540-93662-9).
- 4.2 Claim 15 is not clear, as it is formulated as an independent claim. However, the sole difference to claim 2 appears to be the additional feature, that morpholine is used in excess in step i). Consequently claim 15 should be formulated as a dependent claim, being dependent on claim 2.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

OLSHEMSKI, Stephen
Wilson Sonsini Goodrich & Rosati
650 Page Mill Road
Palo Alto, California 94304
United States of America

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year)
20 February 2023

Applicant's or agent's file reference
50535-721601

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US2022/050436

International filing date
18 November 2022

Applicant
SPRUCE BIOSCIENCES, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau preferably through ePCT, or on paper to:
The International Bureau of WIPO, 34, chemin des Colombettes, 1211 Geneva 20, Switzerland
(Facsimile No.: +41 22 338 82 70)

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to any protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:**
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/ev/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/AU

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PO BOX 200, WODEN ACT 2606, AUSTRALIA
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Anthony Lai
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PATENT COOPERATION TREATY
PCT
INTERNATIONAL SEARCH REPORT
(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 50535-721601		FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2022/050436	International filing date (<i>day/month/year</i>) 18 November 2022	(Earliest) Priority Date (<i>day/month/year</i>) 19 November 2021	
Applicant SPRUCE BIOSCIENCES, INC.			
<p>This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.</p> <p>This international search report consists of a total of 7 sheets.</p> <p>☐ It is also accompanied by a copy of each prior art document cited in this report.</p>			
<p>1. Basis of the report</p> <p>a. With regard to the language, the international search was carried out on the basis of:</p> <p style="margin-left: 40px;">☒ The international application in the language in which it was filed.</p> <p style="margin-left: 40px;">☐ A translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).</p> <p>b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).</p> <p>c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.</p> <p>2. ☐ Certain claims were found unsearchable (See Box No. II).</p> <p>3. ☒ Unity of invention is lacking (See Box No. III).</p> <p>4. With regard to the title,</p> <p style="margin-left: 40px;">☒ the text is approved as submitted by the applicant.</p> <p style="margin-left: 40px;">☐ the text has been established by this Authority to read as follows:</p> <p>5. With regard to the abstract,</p> <p style="margin-left: 40px;">☒ the text is approved as submitted by the applicant.</p> <p style="margin-left: 40px;">☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.</p> <p>6. With regard to the drawings,</p> <p>a. the figure of the drawings to be published with the abstract is Figure No. 1</p> <p style="margin-left: 40px;">☒ as suggested by the applicant.</p> <p style="margin-left: 40px;">☐ as selected by this Authority, because the applicant failed to suggest a figure.</p> <p style="margin-left: 40px;">☐ as selected by this Authority, because this figure better characterizes the invention.</p> <p>b. ☐ none of the figures is to be published with the abstract.</p>			

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.

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	



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	"I" 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
"D" document cited by the applicant in the international application	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search
20 February 2023

Date of mailing of the international search report
20 February 2023

Name and mailing address of the ISA/AU

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/US2022/050436
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 [0125]-[0126]; Examples 2-3	25-55 and 75-105
X	US 2020/0255436 A1 (Spruce Biosciences, Inc.) 13 August 2020 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 JJ, 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. Abstract	25-55 and 75-105
X	WO 2008/036579 A1 (ELI LILLY AND COMPANY) 27 March 2008 Abstract; Example 16	25-55 and 75-105

INTERNATIONAL SEARCH REPORT	International application No. PCT/US2022/050436
Supplemental Box	
<p data-bbox="217 279 464 302">Continuation of: Box III</p> <p data-bbox="217 312 1382 365">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.</p> <p data-bbox="217 388 1422 441">This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:</p> <ul data-bbox="261 464 1458 573" style="list-style-type: none"> <li data-bbox="261 464 1458 516">• 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 <li data-bbox="261 520 1458 573">• 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 <p data-bbox="217 630 1458 709">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.</p> <p data-bbox="217 732 1256 756">When there is no special technical feature common to all the claimed inventions there is no unity of invention.</p> <p data-bbox="217 779 1468 858">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</p> <p data-bbox="217 882 1455 961">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 <i>a priori</i>.</p>	
Form PCT/ISA/210 (Supplemental Box) (July 2019)	

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		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
		CN 114423436 A	29 Apr 2022
		EP 3986416 A1	27 Apr 2022
		JP 2022541550 A	26 Sep 2022
		KR 20220052927 A	28 Apr 2022
		TW 202116324 A	01 May 2021
		US 2022133742 A1	05 May 2022
		US 2020/0255436 A1	13 August 2020
WO 2008/036579 A1	27 March 2008	WO 2008036579 A1	27 Mar 2008
		AR 062886 A1	10 Dec 2008
		AU 2007297421 A1	27 Mar 2008
		AU 2007297421 B2	08 Mar 2012
		BR PI0717023 A2	11 Mar 2014
		BR PI0717023 B1	19 Nov 2019
		CA 2663511 A1	27 Mar 2008
		CL 2007002693 A1	18 Apr 2008
		CN 101516887 A	26 Aug 2009
		CN 101516887 B	02 Nov 2011
		CR 10682 A	13 Aug 2009
		EA 200970303 A1	30 Oct 2009
		EA 015179 B1	30 Jun 2011
		EP 2094709 A1	02 Sep 2009
		EP 2094709 B1	15 Sep 2010
		HK 1132505 A1	26 Feb 2010
		IL 197614 A	31 Oct 2012
		JP 2010504344 A	12 Feb 2010
		JP 5161226 B2	13 Mar 2013
		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.

Form PCT/ISA/210 (Family Annex)(July 2019)

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. 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
		RS 51545 B	30 Jun 2011
		TN 2009000095 A1	19 Aug 2010
		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. Form PCT/ISA/210 (Family Annex)(July 2019)			

PATENT COOPERATION TREATY

From the:
INTERNATIONAL SEARCHING AUTHORITY

To:

OLSHEMSKI, Stephen
Wilson Sonsini Goodrich & Rosati
650 Page Mill Road
Palo Alto, California 94304
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing (*day/month/year*)
20 February 2023

Applicant's or agent's file reference
50535-721601

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2022/050436

International filing date (*day/month/year*)
18 November 2022

Priority date (*day/month/year*)
19 November 2021

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

**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)**

Applicant

SPRUCE BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- | | |
|--|---|
| ☒ Box No. I | Basis of the opinion |
| ☐ Box No. II | Priority |
| ☐ Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☒ Box No. IV | Lack of unity of invention |
| ☒ Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement |
| ☐ Box No. VI | Certain documents cited |
| ☐ Box No. VII | Certain defects in the international application |
| ☒ Box No. VIII | Certain observations on the international application |

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606,
AUSTRALIA
Email address: pct@ipaaustralia.gov.au

Date of completion of this opinion
20 February 2023

Authorised Officer

Anthony Lai
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US2022/050436

Box No. I	Basis of this opinion
1.	With regard to the language , this opinion has been established on the basis of: ☒ The international application in the language in which it was filed ☐ A translation of the international application into, , which is the language of a translation furnished for the purposes of international search (under Rules 12.3(a) and 23.1(b)).
2.	☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43 <i>bis</i> .1(b))
3.	☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of a sequence listing: a. ☐ forming part of the international application as filed. b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)). ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4.	☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5.	Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2022/050436

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

- ☐ complied with
- ☒ not complied with for the following reasons:

See Supplemental Box for Details

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☒ all parts
- ☐ the parts relating to claims Nos.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY		International Application No. PCT/US2022/050436									
Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement										
<p>1. Statement</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%; vertical-align: top;">Novelty (N)</td> <td style="width: 40%; vertical-align: top;"> Claims 1-105 Claims None </td> <td style="width: 30%; vertical-align: top; text-align: center;"> YES NO </td> </tr> <tr> <td style="vertical-align: top;">Inventive step (IS)</td> <td style="vertical-align: top;"> Claims 1-24 and 56-74 Claims 25-55 and 75-105 </td> <td style="vertical-align: top; text-align: center;"> YES NO </td> </tr> <tr> <td style="vertical-align: top;">Industrial applicability (IA)</td> <td style="vertical-align: top;"> Claims 1-105 Claims None </td> <td style="vertical-align: top; text-align: center;"> YES NO </td> </tr> </table>			Novelty (N)	Claims 1-105 Claims None	YES NO	Inventive step (IS)	Claims 1-24 and 56-74 Claims 25-55 and 75-105	YES NO	Industrial applicability (IA)	Claims 1-105 Claims None	YES NO
Novelty (N)	Claims 1-105 Claims None	YES NO									
Inventive step (IS)	Claims 1-24 and 56-74 Claims 25-55 and 75-105	YES NO									
Industrial applicability (IA)	Claims 1-105 Claims None	YES NO									
<p>2. CITATIONS AND EXPLANATIONS:</p> <p><u>CITATIONS</u></p> <p>D1: WO 2021016208 A1 (SPRUCE BIOSCIENCES, INC.) 28 January 2021 D2: US 2020/0255436 A1 (Spruce Biosciences, Inc.) 13 August 2020 D3: Sarafoglou K, Barnes CN, Huang M, Imel EA, Madu JJ, 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. D4: WO 2008/036579 A1 (ELI LILLY AND COMPANY) 27 March 2008</p> <p><u>NOVELTY (N)</u></p> <p><i>Please note that the term 'crystalline' of claims 56-105 has been construed according to the definition provided in the specification (see [0048]), and has been construed to include all crystalline and amorphous forms of a compound.</i></p> <p>Claims 1-105 are novel when compared to the disclosure of any one of D1-D4. These claims meet the requirements of PCT Article 33(2) with respect to novelty.</p> <p><u>INVENTIVE STEP (IS)</u></p> <p>Claims 25-55 and 75-105 do not involve an inventive step when compared to disclosure of any one of D1-D4.</p> <p>D1 discloses methods for treating patients with congenital adrenal hyperplasia (CAH) (see Abstract), comprising administering pharmaceutical compositions comprising tildacerfont (compound 1), or pharmaceutical salts, and excipients such as diluents such as microcrystalline cellulose, monosaccharides such as glucose, and wetting agents such as sodium lauryl sulfate (see [0125]-[0126]; Examples 2-3).</p> <p>D2 discloses formulation for treating diseases comprising CRF antagonist 71.25% (50 mg/tablet) tildacerfont (compound 1), 3% (4.21 mg/tablet) hydroxypropyl cellulose, and 20% (28.07 mg/tablet) microcrystalline cellulose (see Abstract; [0019]; Example 10-12, Table 12 and 15-16)</p> <p>D3 discloses tildacerfont (compound 1), a corticotropin-release factor type-1 (CRF1) receptor antagonist for treating congenital adrenal hyperplasia, wherein patients with 21-hydroxylase deficiency (21OHD) were orally administered tildacerfont (see Abstract).</p> <p>D4 discloses thiazole pyrazolopyrimidines as CRF1 receptor antagonists, such as tildacerfont (compound 1) for treating psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndrome (see Abstract; Example 16).</p>											

The subject matter of independent claims 25 and 55 differ from any one of D1-D4 in that none of D1-D4 disclose dosages forms or compositions comprising amounts of tildacerfont (compound 1) and excipients such as lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium lauryl sulfate, or croscarmellulose sodium. However, The crystal morphology of a compound is known to be the sole contributing factor to the stability of said compound, and the amount of tildacerfont, or excipients, in a formulation do not provide any surprising or unexpected advantages to the invention. These features are considered to be features that a skilled practitioner would optimize using routine trial and error alone. Therefore, the independent claims 25 and 55 add obvious features which a skilled worker would optimize using routine trial and error and without inventive ingenuity.

Furthermore, appended claims 26-54 and 75-105 add features that are either disclosed in any one of D1-D4, or are obvious features that cannot contribute to providing a patentable inventive step. Features such as choice of excipients, and amounts thereof, drug delivery form, and dosing regimen are have not been demonstrated to provide any surprising or unexpected advantages and are also considered to be mere routine modifications. Moreover, features such as methods of treating or preventing tumors, congenital adrenal hyperplasia, hyperandrogenic symptoms, menstrual irregularity, ovulatory dysfunction, infertility, metabolic symptoms, polycystic ovary syndrome, endometriosis or symptoms thereof, and pain and symptoms thereof, have not been demonstrated to provide any surprising or unexpected advantages and are also considered to be obvious to try.

Therefore, the subject matter of all of claims 25-55 and 75-105 are obvious and do not meet the requirements of PCT Article 33(3) for inventive step.

Claims 1-24 and 56-74 do involve an inventive step in view of any one of D1-D4.

The subject matter of independent claims 1, 11, 25, 55, 56 or 69 differ from any one of D1-D4 in that none of D1-D4 disclose X-ray powder diffraction pattern, differential calorimetry thermogram, % amounts of compound 1 or excipients, oxalate salts of compound 1 or preparation methods thereof, and none of D1-D4 teach towards such features.

Therefore, claims 1-24 and 56-74 are not obvious and do meet the requirements of PCT Article 33(3) for inventive step.

INDUSTRIAL APPLICABILITY (IA)

The invention defined in the claims is considered to meet the requirements of Industrial Applicability under Article 33(4) of the PCT because it can be made by, or used in, industry.

<p style="text-align: center;">WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY</p> <p>Box No. VIII Certain observations on the international application</p>	<p>International Application No. PCT/US2022/050436</p>
<p>The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:</p> <p>Claim 1 (and claims dependent thereof) do not comply with PCT Article 5. The description does not disclose the invention in a manner sufficiently clear and complete enough to be carried out by a person skilled in the art. The PCT Guidelines state that the disclosure of the claimed invention is considered sufficiently clear and complete if it provides information which is sufficient to allow the invention to be carried out by a person skilled in the art as of the international filing date, without undue experimentation.</p> <p>The present specification discloses preparation of crystalline compositions comprising 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine/tildacerfont (CRF1 antagonist), wherein the crystalline composition is characterised by X-ray powder diffraction or differential scanning calorimetry (see Examples 1-3). Claim 1 defines a pharmaceutical composition comprising a CRF1 antagonist characterized by an X-ray powder diffraction pattern comprising a peak selected from any one or more of $10.84 \pm 0.2^\circ 2-\theta$, $15.96 \pm 0.2^\circ 2-\theta$, $23.44 \pm 0.2^\circ 2-\theta$, and $24.80 \pm 0.2^\circ 2-\theta$.</p> <p>The claimed invention extends beyond the embodiments disclosed in the specification and encompasses <i>any</i> CRF1 antagonist characterised by the claimed X-ray powder diffraction pattern. However, no other compounds except 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine/tildacerfont has been disclosed in the specification as filed. The crystal morphology of compounds is inherently unpredictable in the art, and therefore, there is no guiding principle which enables a person skilled in the art to work the invention over its full scope. A person skilled in the art is required to conduct their own research into every possible CRF1 antagonist which can produce the claimed X-ray powder diffraction pattern. Therefore, the scope of the claimed invention is unduly broad and lacks a sufficiently clear and complete disclosure to enable a person skilled in the art to perform the full scope of claim 1.</p> <p>A similar objection applies to claim 11 (and claims dependent thereof), wherein the person skilled in the art is required to conduct their own research into every possible CRF1 antagonist which can produce the claimed differential scanning calorimetry thermogram.</p> <p>Similarly, claims 1 and 11 (and claims dependent thereof) do not comply with Article 6 of the PCT because it is not fully supported by the description.</p> <p>The scope of the claimed invention as stated above is not supported across its full scope because it is not reasonable to extrapolate the single embodiment of 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine/tildacerfont to <i>all</i> CRF1 antagonists.</p> <p>Therefore, the search and opinion has been restricted to the CRF1 antagonist enabled by the specification, 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine/tildacerfont, and oxalate salt crystal forms thereof.</p> <p>Claim 93 is not clear, in that it recites '<i>the method of any one of claims 75 to 92, wherein the crystalline composition or the pharmaceutical composition is 75to in a fed state</i>'. For the purposes of this report claim 93 has been construed as '<i>the method of any one of claims 75 to 92, wherein the crystalline composition or the pharmaceutical composition is administered in a fed state</i>'.</p>	

<p style="text-align: center;">WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY</p> <p>Supplemental Box</p>	<p>International Application No. PCT/US2022/050436</p>
<p>Continuation of: Box IV</p> <p>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.</p> <p>This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:</p> <ul style="list-style-type: none"> • 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 <p>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.</p> <p>When there is no special technical feature common to all the claimed inventions there is no unity of invention.</p> <p>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</p> <p>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 <i>a priori</i>.</p>	



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(54) Title: CRF1 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA

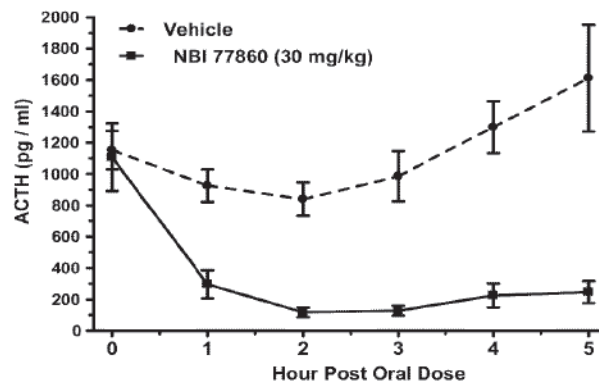


FIG. 2

(57) Abstract: CRF₁ receptor antagonists have the potential to directly inhibit ACTH release in patients with CAH and thereby allow normalization of androgen production while using lower, more physiologic doses of hydrocortisone, and thus reducing treatment-associated side effects.

TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA

BACKGROUND

Technical Field

Compositions and methods for treating congenital adrenal hyperplasia
5 are described herein.

Description of the Related Art

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive genetic disorders that result in little or no cortisol biosynthesis. The most frequent form of the disease is 21-hydroxylase deficiency caused by mutations in the *CYP21A2* gene
10 located on chromosome 6p21, which accounts for approximately 95% of CAH cases (see, e.g., Speiser et al., *Int. J. Pediatr. Endocrinol.* 2010:494173 (2010) for a review). These mutations can range from complete loss of enzyme activity required for synthesis of cortisol in the adrenal cortex to a spectrum of partial loss, which results in disease severity that is a direct consequence of a specific mutation. This continuum of 21-
15 hydroxylase deficiency has been broadly classified into salt-wasting and simple-virilizing forms, grouped as classical CAH, and the milder form known as non-classic CAH (NCCAH) or “late-onset” CAH, which is usually diagnosed in late childhood or early adulthood. Non-classic CAH patients are either homozygous or compound heterozygotes, often with a classical CAH allele. These patients have sufficient enzyme
20 activity (> 20-50% of normal) such that they do not have salt-wasting or cortisol deficiency and have normal genitalia at birth, and many remain asymptomatic throughout life (Trapp et al., *Steroids* 77(4):342-46 (2012)). In the less frequent form of the disease, which accounts for 5% of cases, mutation of the 11 β -hydroxylase gene *CYP11B1* results in CAH (11 β -OH CAH).

25 Both genetic mutations result in congenital adrenal hyperplasia, cortisol deficiency and excessive adrenocorticotrophic hormone (ACTH) production with overproduction of androgens. These patients require lifelong management with

glucocorticoids and the attendant problems associated with such treatment. Accordingly, a significant need exists for treatment regimens to improve the health, well-being, quality of life, and to manage related disorders in patient with CAH.

BRIEF SUMMARY

5 Corticotropin-releasing factor (CRF) activates the CRF₁ receptor, a class B G protein-coupled receptor (GPCR). CRF₁ antagonists have the potential to directly inhibit ACTH release in patients with CAH, thereby allowing normalization of androgen production while using lower, more physiologic doses of hydrocortisone, and reducing treatment-associated side effects.

10 In one embodiment, a method is provided for treating CAH by administering to a subject in need thereof an effective amount of a CRF₁ antagonist, including (but not limited to) bedtime administration.

In a more specific embodiment, the CRF₁ antagonist has a dissociation half-life ($t_{1/2}$) in excess of 30 minutes, and in another embodiment in excess of 40
15 minutes, and in another embodiment in excess of 50 minutes.

Embodiment 1. A method for treating Congenital Adrenal Hyperplasia (CAH) by administering to a subject in need thereof a CRF₁ receptor antagonist having a dissociation half-life in excess of 30 minutes.

Embodiment 2. The method of Embodiment 1 wherein the CRF₁
20 receptor antagonist has a dissociation half-life in excess of 40 minutes.

Embodiment 3. The method of Embodiment 1 wherein the CRF₁ receptor antagonist has a dissociation half-life in excess of 50 minutes.

Embodiment 4. The method of any one of Embodiments 1-3 wherein the CRF₁ receptor antagonist is Compound I (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methoxy)phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-
25 a]pyrimidin-7-amine).

Embodiment 5. The method of any one of Embodiments 1-3 wherein the CRF₁ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543,

antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-e]pyrimidin-4-amine), or DMP904.

Embodiment 6. The method of any one of Embodiments 1-5 wherein the CRF₁ receptor antagonist is administered at bedtime.

5 Embodiment 7. The method of any one of Embodiments 1-6 wherein the CRF₁ receptor antagonist is administered at or before the expected circadian release of ACTH.

Embodiment 8. The method of Embodiment 7 wherein the CRF₁ receptor antagonist is administered 3-4 hours before the expected circadian release of
10 ACTH.

Embodiment 9. A method for reducing 17-OHP and ACTH levels in a subject who has Congenital Adrenal Hyperplasia (CAH), said method comprising administering to the subject a CRF₁ receptor antagonist at bedtime.

Embodiment 10. The method of Embodiment 9, wherein the CRF₁ receptor antagonist is administered at or before the expected circadian release of
15 ACTH.

Embodiment 11. The method of Embodiment 9 or Embodiment 10, wherein the CRF₁ receptor antagonist is administered 3-4 hours before the expected circadian release of ACTH.

20 Embodiment 12. The method of any one of Embodiments 9-11, wherein the CRF₁ receptor antagonist is Compound I (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methyloxy)phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine).

Embodiment 13. The method of any one of Embodiments 9-11, wherein
25 the CRF₁ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-e]pyrimidin-4-amine), or DMP904.

Embodiment 14. A CRF₁ receptor antagonist for use in treating Congenital Adrenal Hyperplasia (CAH), wherein the CRF₁ receptor antagonist has a
30 dissociation half-life in excess of 30 minutes.

Embodiment 15. The CRF₁ receptor antagonist of 14, wherein the CRF₁ receptor antagonist has a dissociation half-life in excess of 40 minutes.

Embodiment 16. The CRF₁ receptor antagonist of Embodiment 14, wherein the CRF₁ receptor antagonist has a dissociation half-life in excess of 50
5 minutes.

Embodiment 17. The CRF₁ receptor antagonist of any one of Embodiments 14-16, wherein the CRF₁ receptor antagonist is Compound I (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methyloxy)phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine).

10 Embodiment 18. The CRF₁ receptor antagonist of any one of Embodiments 14-16, wherein the CRF₁ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-e]pyrimidin-4-amine), or DMP904.

Embodiment 19. The CRF₁ receptor antagonist of any one of
15 Embodiments 14-18, wherein the CRF₁ receptor antagonist is suitable for administration at bedtime.

Embodiment 20. The CRF₁ receptor antagonist of any one of Embodiments 14-19, wherein the CRF₁ receptor antagonist is suitable for administration at or before the expected circadian release of ACTH.

20 Embodiment 21. The CRF₁ receptor antagonist of any one of Embodiments 14-20, wherein the CRF₁ receptor antagonist is suitable for administration 3-4 hours before the expected circadian release of ACTH.

In other embodiments, the methods and uses described above and herein further comprise reducing the amount of a glucocorticoid or mineralocorticoid by at
25 least 10%, 15%, 20%, 30%, 40%, 50%, 60% from the recommended daily dose of GC (such as hydrocortisone (HC), prednisone, prednisolone, dexamethasone, or fludrocortisone) administered to a full grown subject (*e.g.*, a human subject) who has CAH. In other embodiments, the methods and uses described above and herein further comprise reducing the amount of a glucocorticoid or mineralocorticoid by at least 10%,
30 15%, 20%, 30%, 40%, 50%, 60% from the recommended daily dose of GC (*e.g.*,

hydrocortisone) or mineralocorticoid (e.g., fludrocortisone) administered to a growing subject (*e.g.*, a human subject) who has CAH.

These and other embodiments will be apparent upon reference to the following detailed description. To this end, various references are set forth herein that
5 describe in more detail certain background information, procedures, compounds and compositions, and are each hereby incorporated by reference in their entirety.

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the
10 terms have the meaning indicated. Reference throughout this specification to “one embodiment” or “an embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases “in one embodiment” or “in an
15 referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

Also, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to “a non-human animal” may refer to one or
20 more non-human animals, or a plurality of such animals, and reference to “a cell” or “the cell” includes reference to one or more cells and equivalents thereof (*e.g.*, plurality of cells) known to those skilled in the art, and so forth. When steps of a method are described or claimed, and the steps are described as occurring in a particular order, the description of a first step occurring (or being performed) “prior to” (*i.e.*, before) a
25 second step has the same meaning if rewritten to state that the second step occurs (or is performed) “subsequent” to the first step. The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary between 1% and 15% of the stated
30 number or numerical range. It should also be noted that the term “or” is generally

employed in its sense including “and/or” unless the content clearly dictates otherwise. The term, “at least one,” for example, when referring to at least one compound or to at least one composition, has the same meaning and understanding as the term, “one or more.”

5

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic of steroid synthetic pathways in the adrenal gland. The most common form of CAH is caused by 21-hydroxylase (also called 21- α -hydroxylase) deficiency resulting in a decrease of cortisol and increase in androgens such as testosterone and estrogen. A more rare type of classical CAH is 11 β -hydroxylase deficiency.

Figure 2 presents a graph illustrating the effect of Compound I (NBI-77860) on ACTH concentration in adrenalectomized rats. Rats received 30 mg/kg of Compound I (NBI-77860) orally. Data are presented as mean plasma concentration of ACTH ($\pm$ SEM).

Figures 3A-C present graphs illustrating the effect of CRF₁ receptor antagonists, differentiated by their dissociation half-life, on ACTH concentration in adrenalectomized rats.

Figure 4 presents the study design schematic for the clinical trial described in Example 6 that was designed to assess the safety, tolerability and plasma exposure of NBI-77860, as well as the effect of this compound on endogenous levels of HPA (hypothalamic-pituitary-adrenal) axis hormones.

Figure 5 presents the data for mean 17-OHP (upper panel) and ACTH levels (lower panel) throughout the 24-hour postdose period for the clinical trial described in Example 6.

Figure 6 presents the response of a specific individual subject for 17-OHP (upper panel) and ACTH levels (lower panel) following administration of 300 mg and 600 mg NBI-77860 and placebo over time.

DETAILED DESCRIPTION

As described herein, CRF₁ receptor antagonists have been found to directly inhibit ACTH release in patients with CAH and thereby allow normalization of androgen production. Administration of a CRF₁ receptor antagonist permits use of
5 lower, more physiologic doses of hydrocortisone in subjects with CAH and thus reduces treatment-associated side effects.

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
10 dissociation-enhanced lanthanide fluoroimmunoassay (DELFI; 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
15 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
20 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%.

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
25 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.

Treatment of CAH is based on normalization of hormone and steroid
30 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.

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. 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.*, Finkelstein et al., *J. Clin. Endocrinol Metab.* 97(12):4429-38 (2012)).

Treatment of CAH includes efforts to normalize the cortisol deficiency with glucocorticoids (usually hydrocortisone 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
5 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.,* Elneceve 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)).
10

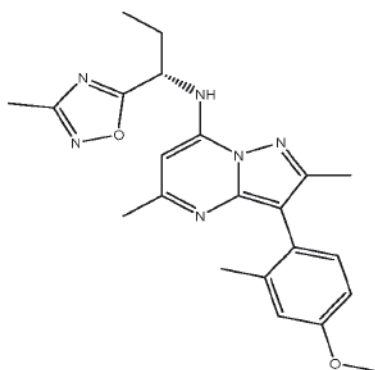
Corticotropin-releasing factor (CRF) was isolated from ovine hypothalami and identified as a 41-amino acid peptide. CRF has been found to produce
15 profound alterations in endocrine, nervous, and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotrophic 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
20 from corticotrophs in the anterior pituitary via binding to the CRF₁ receptor, a member of the class B family of G-protein coupled receptors.

Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF₁ receptor binding activity and which are capable of antagonizing the CRF₁ receptor remains a desirable goal and
25 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.

The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the
30 synthesis of pregnenolone initiating steroidogenesis in the adrenal gland (*see* Figure 1).

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.

In an embodiment, a CRF₁ receptor antagonist useful for the treatment of CAH is NBI-77860, 2,5-dimethyl-3-[2-methyl-4-(methoxy)phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine (also referred to as "Compound I" herein), and which has the following structure.



Compound I

Compound I is a potent CRF₁ antagonist possessing a binding pK_i = 8.2 (see, e.g., Tellew et al., *Bioorg. Med. Chem. Lett.* 20:7259, 2010 and Int'l. Patent Appl. Publ. No. WO 2006/044958, both of which references are incorporated by reference herein in their entirety). As described herein, Compound I has potent ACTH lowering
5 effects as shown in adrenalectomized rats.

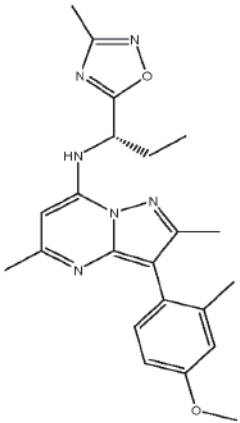
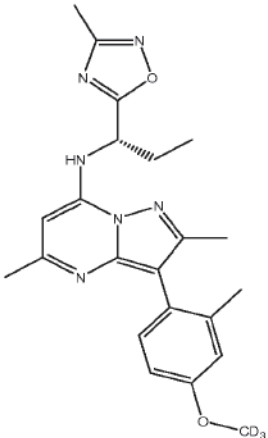
In another embodiment, the CRF₁ receptor antagonist useful for the treatment of CAH is a small molecule antagonist as described in U.S. 6,586,456, US 6,806,282, US 6,531,475, US 6,664,261, US 6,610,678, WO 98/08846, WO 98/11075, WO 99/10350, WO 2000/059888, WO 2006/044821, WO 2006/102194, WO
10 2006/107784, WO 2006/116412, WO 2006/126718, WO 2007/069565, WO 2007/069671, WO 2008/036541, WO 2008/036579, WO 2008/051533, WO 2008/082003, WO 2008/083070, WO 2008/136377, WO 2009/008552, WO 2009/144632, WO 2010/014280, WO 2010/014687, WO 2010/015628, WO 2010/015655, WO 2010/062718, WO 2010/096426, WO 2011/043387, WO
15 2011/092293, WO 2011/095450, WO 2011/092290, and WO 2011/043381.

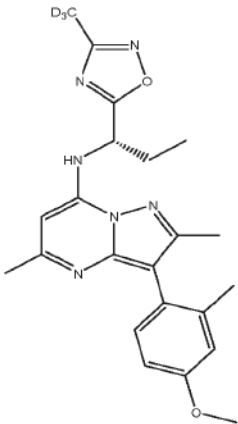
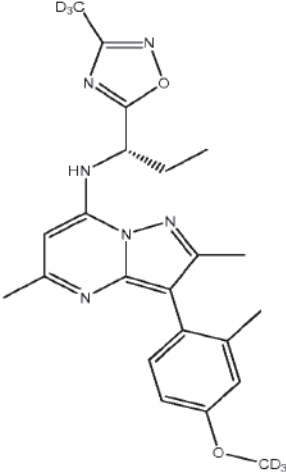
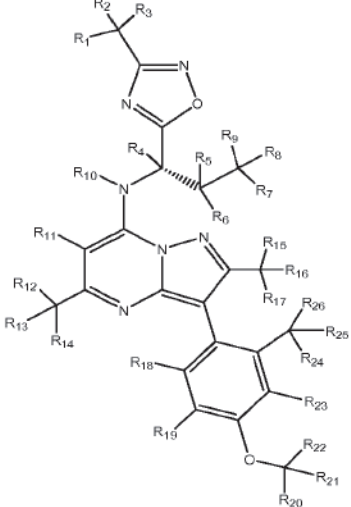
In still another embodiment, the CRF₁ receptor antagonist is NBI-30775, CP-316,311, pexacerfont, emicerfont, SSR-125543 [4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine], SSR-126374, ONO-2333, NBI-34041, JNJ-19567470,
20 GSK586529, PF-00572778, CP-376395, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-e]pyrimidin-4-amine), and DMP904.

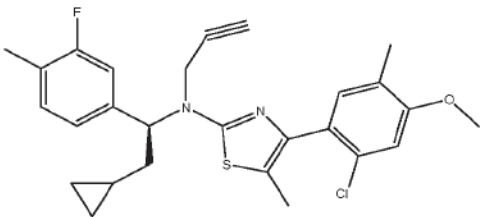
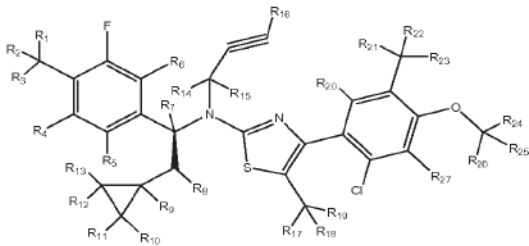
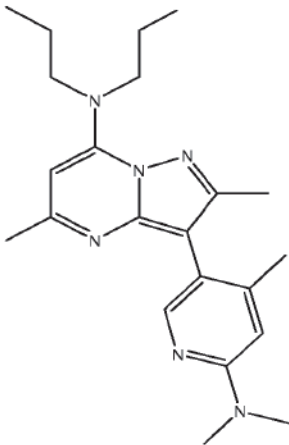
In yet another embodiment, the CRF₁ receptor antagonist has a dissociation half-life ($t_{1/2}$) in excess of 30 minutes, and in another embodiment in excess of 40 minutes, and in another embodiment in excess of 50 minutes. The dissociation
25 half-life of a particular CRF₁ receptor antagonist is determined by the technique disclosed in Example 3. Representative CRF₁ receptor antagonists of these embodiments include Compound I, NBI-30775, NBI-34041, SSR-125543A, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-e]pyrimidin-4-amine), and DMP904.

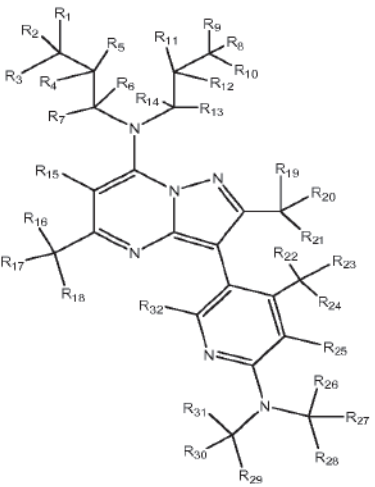
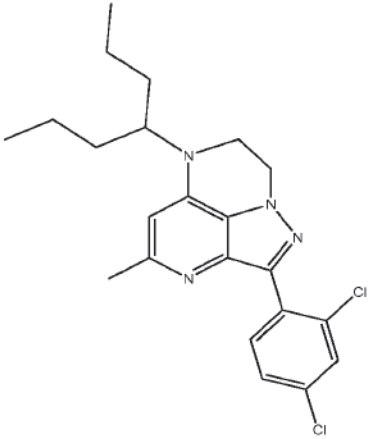
With respect to the compounds described herein, it should also be understood that when a particular position is designated as hydrogen, that such hydrogen (H) may be replaced with deuterium (D). Incorporation of deuterium in place of hydrogen is known to produce significant effects on the physiological and pharmacological activities of the substituted compound. To this end, it should be understood that deuterium replacement of hydrogen means that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium. Accordingly, in one embodiment representative compounds include the following.

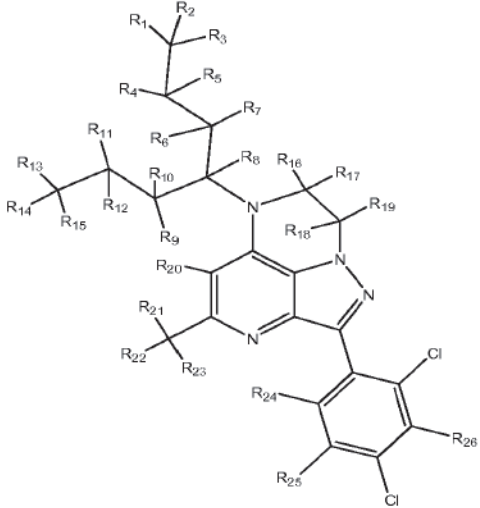
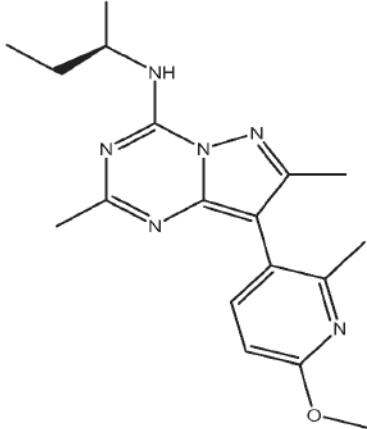
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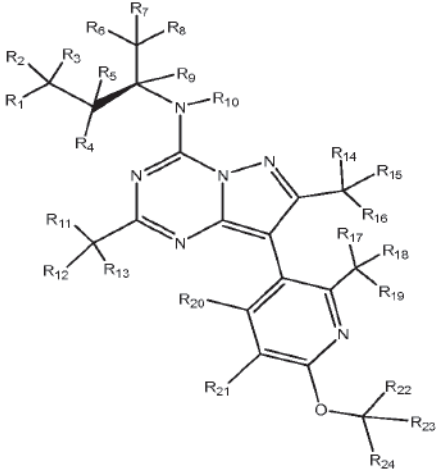
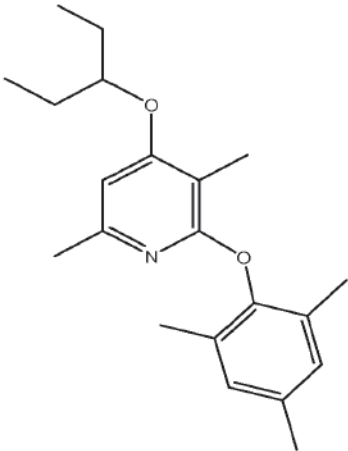
Cpd.	Structure	Chemical Name
NBI-77860		2,5-dimethyl-3-[2-methyl-4-(methyloxy)phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine
Deuterated NBI-77860		2,5-dimethyl-3-[2-methyl-4-(d ₃ -methyloxy)phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine

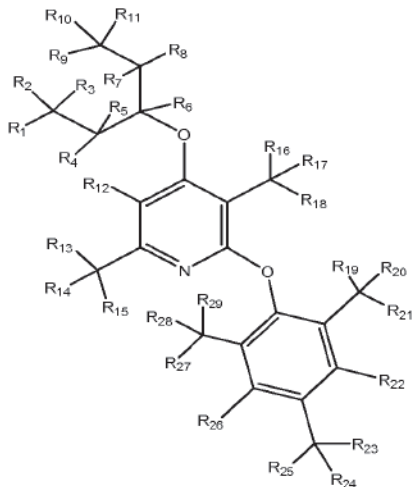
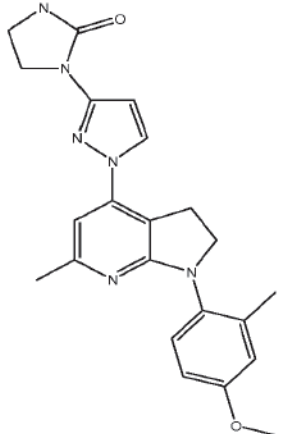
Cpd.	Structure	Chemical Name
Deuterated NBI-77860	 <p>The structure shows a pyrazolo[1,5-a]pyrimidin-7-amine core. At position 1, there is a (1S)-1-(3-d₃-methyl-1,2,4-oxadiazol-5-yl)propyl group. At position 5, there is a 2-methyl-4-(d₃-methoxy)phenyl group. The pyrimidine ring has methyl groups at positions 2 and 6.</p>	2,5-dimethyl-3-[2-methyl-4-(methyloxy)phenyl]-N-[(1S)-1-(3-d ₃ -methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine
Deuterated NBI-77860	 <p>The structure is identical to the one above, but the methoxy group on the phenyl ring is labeled as O-CD₃, indicating it is a deuterated methoxy group.</p>	2,5-dimethyl-3-[2-methyl-4-(d ₃ -methyloxy)phenyl]-N-[(1S)-1-(3-d ₃ -methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine
Deuterated NBI-77860	 <p>The structure shows the same core as the previous two, but with various R groups (R₁ through R₂₅) attached to different positions on the molecule, representing a general deuterated structure.</p>	

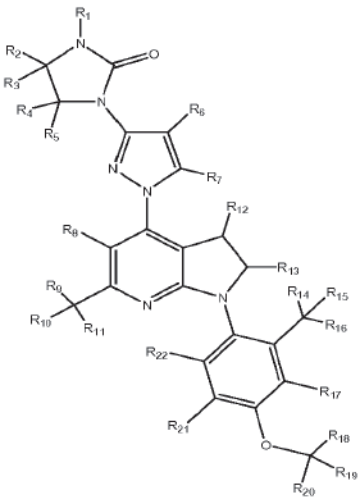
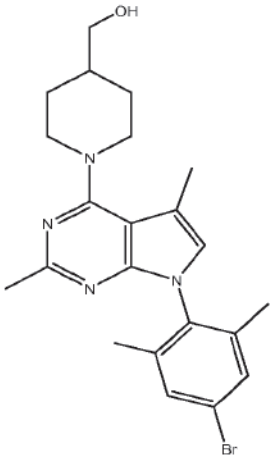
Cpd.	Structure	Chemical Name
	R ₁ -R ₂₆ independently H or D	
SSR-125543		4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine
Deuterated SSR-125543	 <p>R₁-R₂₇ independently H or D</p>	
NBI-30775		5-[7-(diethylamino)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-3-yl]-N,N,4-trimethylpyridin-2-amine

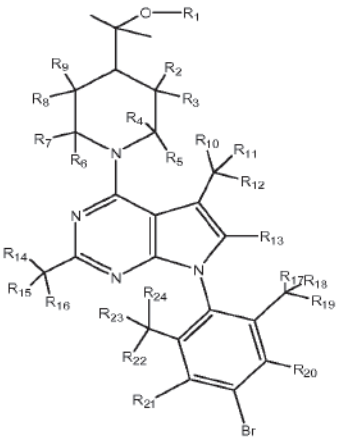
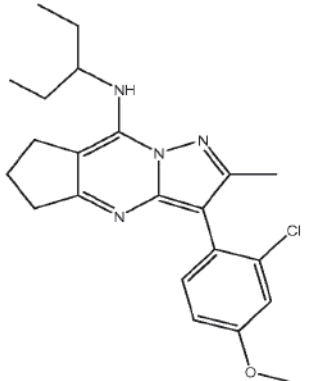
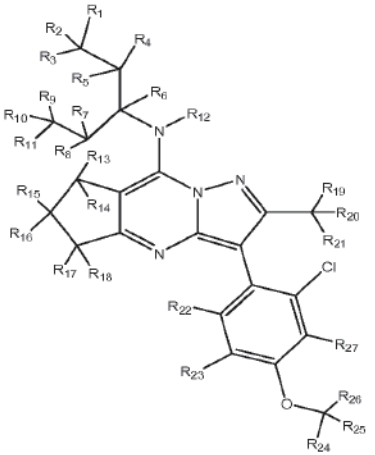
Cpd.	Structure	Chemical Name
Deuterated NBI-30775	 <p>R₁-R₃₂ independently H or D</p>	
NBI-34041		3-(2,4-dichlorophenyl)- 9-(heptan-4-yl)-6- methyl- 1,2,5,9- tetraazatricyclo[6.3.1.0 ^{4,12}] dodeca- 2,4(12),5,7- tetraene

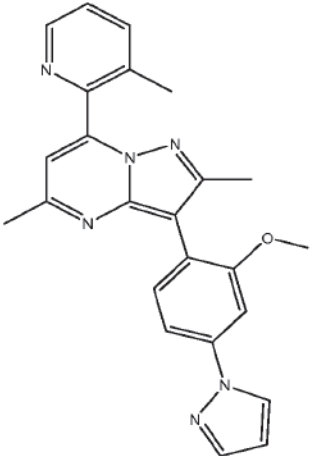
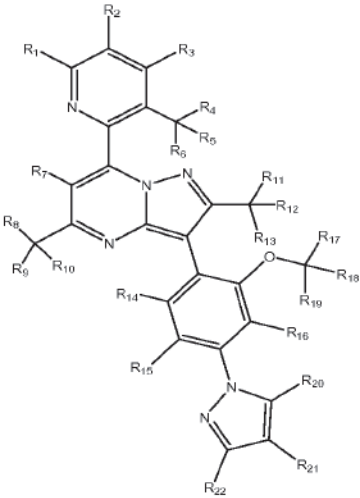
Cpd.	Structure	Chemical Name
Deuterated NBI-34041	 <p>R₁-R₂₆ independently H or D</p>	
Pexacerfont		N-[(2R)-butan-2-yl]-8-(6-methoxy-2-methylpyridin-3-yl)-2,7-dimethylpyrazolo[1,5-a][1,3,5]triazin-4-amine

Cpd.	Structure	Chemical Name
Deuterated Pexacerfont	 <p>R₁-R₂₄ independently H or D</p>	
CP-316,311		3,6-dimethyl-4-(pentan-3-yloxy)-2-(2,4,6-trimethylphenoxy)pyridine

Cpd.	Structure	Chemical Name
Deuterated CP-316,311	 <p>R₁-R₂₉ independently H or D</p>	
GSK876008		

Cpd.	Structure	Chemical Name
Deuterated GSK876008	 <p>R₁-R₂₂ independently H or D</p>	
CRA5626/R3 17573		

Cpd.	Structure	Chemical Name
Deuterated CRA5626/R3 17573	 <p>R₁-R₂₄ independently H or D</p>	
ONO2333Ms		10-(2-chloro-4-methoxyphenyl)-11-methyl-N-(pentan-3-yl)-1,8,12-triazatricyclo[7.3.0.0 ^{3,7}]dodeca-2,7,9,11-tetraen-2-amine
Deuterated ONO2333	 <p>R₁-R₂₇ independently H or D</p>	

Cpd.	Structure	Chemical Name
NBI76169		
Deuterated NBI76169	 <p data-bbox="613 1291 971 1327">R_1-R_{22} independently H or D</p>	

In another embodiment, any of the aforementioned compounds may incorporate stable or radioactive isotopes. Accordingly, also contemplated is use of isotopically-labeled compounds identical to those described herein, wherein one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into these compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to

deuterium as discussed above (2H), as well as 3H, 13C, 14C, 15N, 18O, 17O, 31P, 32P, 35S, 18F, and 36Cl, respectively. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as 3H and 14C are incorporated, are also useful in drug or substrate tissue distribution assays. Tritiated hydrogen (3H) and carbon-14 (14C) isotopes are particularly preferred for their ease of preparation and detectability. Substitution with heavier isotopes such as deuterium (2H) can provide certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dose requirements and, therefore, may be preferred in some circumstances. Isotopically-labeled compounds can generally be prepared by performing procedures routinely practiced in the art.

Effect on Plasma ACTH in Adrenalectomized Rats

Adrenalectomy eliminates circulating corticosterone (the primary glucocorticoid) in rats and removes the negative feedback control of the HPA axis at both the hypothalamic and pituitary (corticotroph cells) levels and thus chronically elevates plasma ACTH (*see, e.g., Mims et al., J. Natl. Med. Assoc.* 69:145-47 (1977)). Intravenous injection of peptide CRF₁ receptor antagonists have been demonstrated to reduce the high plasma ACTH levels in adrenalectomized (ADX) rats (*see, e.g., Rivier et al., J. Med. Chem.* 12:42:3175-82 (1999)). These findings were recapitulated with the small molecule NBI-77860 (Compound I). In adrenalectomized rats, Compound I has potent capability for lowering ACTH. The maximum reduction in ACTH correlated with peak plasma concentrations of NBI-77860; however, the duration of the ACTH-lowering effect exceeded drug plasma exposure. In adrenalectomized rats, a predictable relationship therefore exists between integrated plasma exposure of NBI-77860 and *in vivo* efficacy following oral administration.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. CRF antagonists described herein may be capable of inhibiting the specific binding of CRF to its receptor and consequently antagonizing activities associated with CRF. A compound may be assessed for activity as a CRF antagonist by one or more generally accepted assays including the assay

described in the Examples. CRF antagonists useful for the methods described herein include compounds that demonstrate affinity for CRF receptor.

Without wishing to be bound by theory, in the treatment of CAH, CRF receptor antagonists would potentially block the release of ACTH from pituitary corticotrophs, thereby decreasing the production of androgens, and allow a more refined treatment paradigm for replacement of cortisol. Animal and human studies have shown the pharmacologic effect of Compound I (NBI-77860) on ACTH release. Standard biomarker assessments used by endocrinologists when monitoring treatment efficacy may be used for monitoring the effects of this CRF₁ receptor antagonist. Plasma levels of 17-OHP, androstenedione, testosterone, cortisol and ACTH, as well as urinary metabolites of these steroids, are easily measured in both children and adults giving rapid and meaningful data regarding treatment impact.

Pharmaceutical Compositions and Methods of Treatment

The present disclosure further provides for pharmaceutical compositions comprising any one of the CRF antagonist compounds described herein and a pharmaceutically acceptable excipient for use in the methods for treating CAH. A pharmaceutically acceptable excipient is a physiologically and pharmaceutically suitable non-toxic and inactive material or ingredient that does not interfere with the activity of the active ingredient; an excipient also may be called a carrier. The CRF antagonist compounds may be formulated in a pharmaceutical composition for use in treatment or preventive (or prophylactic) treatment (*e.g.*, reducing exacerbation of CAH disease, or occurrence or recurrence of one or more symptoms of the disease). The methods and excipients described herein are exemplary and are in no way limiting. Pharmaceutically acceptable excipients are well known in the pharmaceutical art and described, for example, in Rowe *et al.*, Handbook of Pharmaceutical Excipients: A Comprehensive Guide to Uses, Properties, and Safety, 5th Ed., 2006, and in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)). Examples of pharmaceutically acceptable excipients include sterile saline and phosphate buffered saline at physiological pH. Preservatives, stabilizers, dyes, buffers,

and the like may be provided in the pharmaceutical composition. In addition, antioxidants and suspending agents may also be used.

Therapeutic and/or prophylactic benefit includes, for example, an improved clinical outcome, both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow or retard (lessen) an undesired physiological change or disorder, or to prevent or slow or retard (lessen) the expansion or severity of such disorder. As discussed herein, beneficial or desired clinical results from treating a subject include, but are not limited to, abatement, lessening, or alleviation of symptoms that result from or are associated the disease, condition, or disorder to be treated; decreased occurrence of symptoms; improved quality of life; longer disease-free status (*i.e.*, decreasing the likelihood or the propensity that a subject will present symptoms on the basis of which a diagnosis of a disease is made); diminishment of extent of disease; stabilized (*i.e.*, not worsening) state of disease; delay or slowing of disease progression; amelioration or palliation of the disease state; and remission (whether partial or total), whether detectable or undetectable; and/or overall survival. "Treatment" can also mean prolonging survival when compared to expected survival if a subject were not receiving treatment. Subjects in need of treatment include those who already have the condition or disorder as well as subjects prone to have or at risk of developing the disease, condition, or disorder, and those in which the disease, condition, or disorder is to be prevented (*i.e.*, decreasing the likelihood of occurrence of the disease, disorder, or condition). A subject may be a human or non-human mammal (e.g., rat, mouse, dog, cat, livestock, zoo animal).

Optimal doses may generally be determined using experimental models and/or clinical trials. The optimal dose may depend upon the body mass, weight, or blood volume of the subject. In general, the amount of a compound described herein, that is present in a dose ranges from about 0.1 mg to about 30 mg per kg weight of the subject. In certain embodiments, a single dose is about 50-1000 mg. The use of the minimum dose that is sufficient to provide effective therapy is usually preferred. Subjects may generally be monitored for therapeutic effectiveness by clinical evaluation and using assays suitable for the condition being treated or

prevented, which assays will be familiar to those having ordinary skill in the art and are described herein. The level of a compound that is administered to a subject may be monitored by determining the level of the compound in a biological fluid, for example, in the blood, blood fraction (*e.g.*, serum), and/or in the urine, and/or other
5 biological sample from the subject. Any method practiced in the art to detect the compound may be used to measure the level of compound during the course of a therapeutic regimen.

The dose of a composition comprising at least one of the compounds described herein for treating CAH or a related disease or disorder may depend upon the
10 subject's condition, that is, stage of the disease, severity of symptoms caused by the disease, general health status, as well as age, gender, and weight, and other factors apparent to a person skilled in the medical art. Similarly, the dose of the compound may be determined according to parameters understood by a person skilled in the medical art.

15 The pharmaceutical compositions described herein that comprise at least one of the CRF₁ antagonist compounds described herein may be administered to a subject in need by any one of several routes that effectively deliver an effective amount of the compound. Such administrative routes include, for example, oral, parenteral, enteral, rectal, intranasal, buccal, sublingual, intramuscular, and transdermal.
20 Compositions administered by these routes of administration and others are described in greater detail herein.

Administration of the compounds or compositions disclosed includes nighttime administration or administration prior to sleep (*i.e.*, bedtime administration). As used herein, bedtime administration refers to dosing intended to deliver clinically
25 relevant concentrations of the CRF₁ antagonist at or before (such as 2-5 hours before) the expected circadian release of ACTH. Since this ACTH release is typically at 1-2 A.M., and since most orally administered drugs have a T_{max} of several hours, dosing at 10 P.M., for example, which is 3-4 hours in advance of the expected circadian release of ACTH is desirable. This same pre-pulse bedtime dosing may be adapted for shift
30 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 ACTH, and can vary depending upon the individual's (*i.e.*, subject, patient) particular work and sleep patterns. In certain embodiments, a CRF₁ receptor antagonist described herein (for example, NBI-77860 or
5 any one of NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-e]pyrimidin-4-amine), or DMP904) is administered between about 2-5 hours prior to (*i.e.*, before, in advance of) the expected circadian release of ACTH. In other embodiments, the CRF₁ receptor antagonist is administered to the subject between about 2-4 hours or 3-5 hours prior to
10 the expected circadian release of ACTH. In a more specific embodiment, CRF₁ receptor antagonist is administered to the subject between about 3-4 hours prior to the expected circadian release of ACTH.

Also provided herein is a method for reducing 17-OHP and/or ACTH levels in a subject (*i.e.*, patient, individual) who has CAH by administering a CRF₁
15 receptor antagonist. In certain embodiments, the antagonist is administered at or before the expected circadian release of ACTH. In other certain embodiments, the CRF₁ receptor antagonist is administered between about 2-4 hours or between about 3-5 hours prior to the expected circadian release of ACTH. In a more specific embodiment, CRF₁ receptor antagonist is administered to the subject between about 3-4 hours prior
20 to the expected circadian release of ACTH.

The methods described herein that comprise administering a CRF₁ receptor antagonist to a female subject in need thereof in the manner described herein that causes a decrease in level of ACTH and 17-OHP in the subject may result in decreased release of androgens such as testosterone and androstenedione. The dose of
25 glucocorticoids may concomitantly be decreased by a clinically significant amount, which in turn results in decreased side effects.

The amount of glucocorticoids (GC) and mineralocorticoids (MC) for maintenance therapy in patients who have CAH and who are young and growing and for maintenance therapy in patients who are full grown patients is known to a person
30 skilled in the art. For example, guidelines are described in Speiser et al. (*J. Clin.*

Endocrinol. Metab. 95:4133-60 (2010), incorporated by reference in its entirety) and shown in the Tables 1 and 2 therein. Particularly, for young, growing patients who have CAH, persons skilled in the art appreciate that too high dosing with GCs can impede statural growth in the patient. Accordingly, the methods described herein for
5 treating a patient with a CRF₁ receptor antagonist may comprise reducing the dose of a GC in a clinically significant manner.

In certain embodiments, methods for treating CAH by administering a CRF₁ receptor antagonist may further comprise administering a GC at a dose lower than the currently recommended dose of a GC for treating a subject who has CAH. When
10 the subject is a fully grown patient, the dose of a GC, such as the dose of hydrocortisone (HC), prednisone, prednisolone, dexamethasone, or fludrocortisone recommended for maintenance therapy in a fully grown subject may be decreased by about 10%, 15%, 20%, 30%, 40%, 50%, 60% or more from the recommended doses of 15-25 mg/day HC; 5-7.5 mg/day prednisone, 4-6 mg/day prednisolone; 0.25-0.5 mg/day
15 dexamethasone, or 0.05-0.2 mg/day of fludrocortisone. In a subject who is a growing patient with CAH, the recommended dose of GCs, such as HC may be decreased from the total recommended dose of 10-15 mg/m² per day and/or the total dose of fludrocortisone of 0.05-0.2 mg/day may each be decreased by about 10%, 15%, 20%, 30%, 40%, 50%, 60% or more in a subject who receives a CRF₁ receptor antagonist as
20 described herein. In an embodiment, the methods described herein comprising administering to a subject in need thereof an effective amount of a CRF₁ antagonist results in a clinically significant reduction of ACTH levels relative to placebo. In a specific embodiment, administering to a subject in need thereof an effective amount of a CRF₁ antagonist results in a clinically significant reduction of ACTH levels relative to
25 placebo, wherein that reduction is at least 25%. In another embodiment, administering to a subject in need thereof an effective amount of a CRF₁ antagonist results in a clinically significant reduction of ACTH levels relative to placebo, wherein that reduction is at least 50%. See Speiser et al., *supra*, for guidelines regarding administering glucocorticoids and mineralocorticoids.

In another embodiment, the methods described herein comprising administering to a subject in need thereof an effective amount of a CRF₁ antagonist results in a clinically significant reduction of 17-OHP levels relative to placebo. In another specific embodiment, administering to a subject in need thereof an effective
5 amount of a CRF₁ antagonist results in a clinically significant reduction of 17-OHP levels relative to placebo wherein that reduction is at least 25%. In still another embodiment, administering to a subject in need thereof an effective amount of a CRF₁ antagonist results in a clinically significant reduction of 17-OHP levels relative to placebo wherein that reduction is at least 50%.

10 In an embodiment, the methods described herein comprising administering to a subject in need thereof an effective amount of a CRF₁ antagonist results in a clinically significant reduction of both ACTH and 17-OHP levels relative to placebo. In a certain embodiment, administering to a subject in need thereof an effective amount of a CRF₁ antagonist results in a clinically significant reduction of
15 both ACTH and 17-OHP levels relative to placebo wherein the reduction is at least 25%. In another specific embodiment, administering to a subject in need thereof an effective amount of a CRF₁ antagonist results in a clinically significant reduction of both ACTH and 17-OHP levels relative to placebo wherein the reduction is at least 50%.

20 The pharmaceutical compositions may be in the form of a solution. Alternatively, they may be in the form of a solid, such as powder, tablets, or the like. A composition comprising any one of the compounds described herein may be formulated for sustained or slow release. Such compositions may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous
25 implantation, or by implantation at the desired target site. Sustained-release formulations may contain the compound dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Excipients for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The
30 amount of active compound contained within a sustained release formulation depends

upon the site of implantation, the rate and expected duration of release, and the nature of the condition to be treated or prevented.

For oral formulations, at least one of the compounds described herein can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, for example, with conventional additives, such as lactose, mannitol, corn starch or potato starch; with binders; with disintegrators; with lubricants; and if desired, with diluents, buffering agents, moistening agents, preservatives, coloring agents, and flavoring agents. The compounds may be formulated with a buffering agent to provide for protection of the compound from low pH of the gastric environment and/or an enteric coating. A compound included in the compositions may be formulated for oral delivery with a flavoring agent, *e.g.*, in a liquid, solid or semi-solid formulation and/or with an enteric coating. Oral formulations may be provided as gelatin capsules, which may contain the active compound along with powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar carriers and diluents may be used to make compressed tablets.

EXAMPLES

EXAMPLE 1

CRF RECEPTOR BINDING ACTIVITY

CRF antagonists as used in the methods described herein may be evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by Grigoriadis et al. (*see, e.g., Mol. Pharmacol* vol 50, pp 679-686, 1996) and Hoare et al. (*see, e.g., Mol. Pharmacol* 63: 751-765, 2003.) By utilizing radiolabeled CRF ligands, the assay may be used to evaluate the binding activity of the compounds described herein 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 1-10 μ g 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, 2 mM EGTA) containing compound of interest or a reference ligand (for example, sauvagine, urocortin I, or CRF), 0.05 mL of [¹²⁵I] 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 hours 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 ¹²⁵I) 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 XLfit (ID Business Solutions Ltd).

EXAMPLE 2

CRF₁ RECEPTOR AGONIST ACTIVITY

As reported in Fleck *et al.* (*J. Pharmacology and Experimental Therapeutics*, 341(2):518-531, 2012) (hereinafter "Fleck *et al.*" and incorporated by reference in it's entirety) the activity of previously identified CRF₁ receptor antagonists are presented. Such activity is reported as the kinetically derived affinity (K_i) calculated from the association (*k*₁) and dissociation (*k*₋₁) rate constants by the following equation:

$$K_i = k_{-1}/k_1$$

Also as reported in Fleck *et al.*, the kinetic K_i of the CRF₁ receptor antagonists listed in Table 1 below have been reported:

Table 1
Representative CRF₁ Receptor Antagonists

Ligand	<i>k</i> ₁ (10 ⁶ M ⁻¹ min ⁻¹)	Kinetic K _i (nM)
NBI-27914	9.4 ± 3	25

Ligand	k_1 ($10^6 \text{M}^{-1} \text{min}^{-1}$)	Kinetic K_i (nM)
CP-316,311	13 ± 2	12
NBI-46200	6.2 ± 2	22
DMP696	7.7 ± 2	9.5
pexacerfont	2.6 ± 0.1	19
NBI-35965	20 ± 2	2.3
ONO-2333Ms	4.4 ± 2.2	15
antalarmin	3.4 ± 0.6	3.9
NBI-34041	8.3 ± 2.0	1.7
DMP904	18 ± 1	0.38
NBI-30775	14 ± 2.0	0.36
SSR125543A	33 ± 5	0.049

By this same technique, the kinetic K_i of Compound I (NBI-77860) was found to be as follows:

Table 1 (cont.)

Ligand	k_1 ($10^6 \text{M}^{-1} \text{min}^{-1}$)	Kinetic K_i (nM)
NBI-77860	0.24 ± 0.05	48 ± 9

5

EXAMPLE 3

DISSOCIATION HALF-LIFE ($T_{1/2}$) OF CRF₁ RECEPTOR ANTAGONISTS

The dissociation half-life ($t_{1/2}$) of a CRF₁ receptor antagonist as used in the methods described herein is evaluated by the technique described in Fleck *et al.* As described therein, the dissociation rate constant for labeled and unlabeled ligands is

denoted as k_{-1} , while the half-life of drug dissociation from the receptor ($t_{1/2}$), which is equal to the median residence time, is calculated from the dissociation rate constant (k_{-1}) by the following equation:

$$t_{1/2} = 0.693/k_{-1}$$

- 5 As reported in Fleck *et al.*, the dissociation half-life ($t_{1/2}$) of the CRF₁ receptor antagonists listed in Table 2 below have been reported.

Table 2
Dissociation Half-Life of Representative Compounds

Ligand	k_{-1} (min ⁻¹)	Dissociation $t_{1/2}$ (min)
NBI 27914	0.27 ± 0.07	2.6
CP-316,311	0.17 ± 0.04	4.1
NBI-46200	0.13 ± 0.002	5.3
DMP696	0.095 ± 0.02	7.3
pexacerfont	0.049 ± 0.001	14
NBI-35965	0.048 ± 0.005	16
ONO-2333Ms	0.063 ± 0.029	17
antalarmin	0.013 ± 0.002	53
NBI-34041	0.013 ± 0.002	53
DMP904	0.0072 ± 0.002	96
NBI-30775	0.0054 ± 0.0006	130
SSR125543A	0.0016 ± 0.0003	430

- 10 By this same technique, the dissociation half-life of Compound I (NBI-77860) was found to be as follows.

Table 2 (cont.)

Ligand	k_{-1} , min ⁻¹	Dissociation $t_{1/2}$, min
NBI-77860	0.012 ± 0.0003	58

Accordingly, CRF₁ receptor antagonists that have a dissociation half-life ($t_{1/2}$) in excess of 30 minutes include (but are not limited to) antalarim, NBI-34041, DMP904, NBI-30775, SSR125543A, and NBI-77860 (Compound I). These same compounds are also representative of CRF₁ receptor antagonists having a dissociation half-life ($t_{1/2}$) in excess of 40 minutes, and a dissociation half-life ($t_{1/2}$) in excess of 50 minutes.

EXAMPLE 4

10 LOWERING OF ACTH IN ADRENALECTOMIZED RATS

Compound I (NBI-77860) (*see, e.g.,* Tellew et al., *Bioorg. Med. Chem. Lett.* 2010, 20:7259; WO2006044958) is a potent CRF₁ antagonist possessing a binding pK_i of 8.2, a kinetic K_i of 49 nM (Table 1 above), and a Dissociation $t_{1/2}$ of 58 minutes (Table 2 above).

15 Intravenous injection of peptide CRF₁ receptor antagonists have been demonstrated to reduce the high plasma ACTH levels in adrenalectomized (ADX) rats (*see, e.g.,* Rivier et al., *J. Med. Chem.* 12:42:3175-82 (1999)). These findings were recapitulated with the small molecule NBI-77860. When administered orally to ADX rats (n=6/group), 30 mg/kg single doses of NBI-77860 significantly lowered the plasma
20 ACTH levels for up to 5 hours (*see* Figure 2). The duration of efficacy correlated with peak plasma concentrations, with a time course exceeding drug plasma exposure. In adrenalectomized rats, a predictable relationship exists between integrated plasma exposure of NBI-77860 and *in vivo* efficacy following oral administration.

Fleck *et al.* also report the effects of CRF₁ receptor antagonists
25 differentiated by their dissociation half-life on plasma ACTH levels in adrenalectomized rats; namely, NBI 30775, NBI 34041 and NBI 35965. At the highest

dose (10 mg/kg), all three ligands reduced ACTH acutely (1 hr post-injection, Figure 3A-C). After a longer duration, a clear difference emerged between NBI 35965 and the other two ligands. The ACTH level returned to the vehicle level by 2 hr for NBI 35965 (Fig. 3C), whereas the response was sustained for 4-6 hr for NBI 30775 and NBI 34041 (Fig. 3A and 3B).

EXAMPLE 5

PHARMACODYNAMIC EFFECTS OF COMPOUND I IN HUMANS

In this study, pharmacodynamic effects of NBI-77860 (Compound I) on human subjects were evaluated by observing the effect of single oral doses on HPA axis response produced by metyrapone (0.04 g/kg) with respect to placebo and to a single dose of alprazolam (0.75 mg). Metyrapone blocks cortisol synthesis in the adrenal, thereby mimicking the cortisol deficiency of CAH, and is associated with an acute reflex rise ACTH levels.

The primary analysis was performed by determining the ACTH values between 30 min and 4 h post dose (AUC (30 min to 4 h)). In this analysis, when compared to placebo, the following observations were made. A significant reduction of ACTH AUC (30 min to 4 h) was observed with the alprazolam and the NBI-77860, 400 mg treatments. A non-significant reduction in ACTH AUC (30 min to 4 h) was seen with the NBI-77860, 50 mg treatment. An increase in AUC (30 min to 4 h) was seen with the NBI-77860, 10 mg treatment.

In the analysis performed on the ACTH values between 2 h to 4 h post-dose (AUC (2 h to 4 h)) (the period when exposure reached the C_{max} value), there was a significant reduction of ACTH levels in the NBI-77860, 400 mg and 50 mg treatment periods compared with the placebo treatment period; however, the reduction was not seen with the NBI-77860 at the 10 mg dose.

EXAMPLE 6

CLINICAL STUDY

In this study, NBI-77860 (Compound I) was evaluated in the clinical study entitled “A Phase 1, Single-Blind, Placebo-Controlled, Fixed-Sequence, Single-Dose Study to Evaluate the Safety and Tolerability of NBI-77860 in Adult Females with Congenital Adrenal Hyperplasia” (IND 117,388). The study was a single-blind, placebo-controlled, single center, fixed-sequence, single-dose clinical trial in adult female classical CAH patients. It was designed to assess the safety, tolerability, and plasma exposure of NBI-77860, as well as the effect of this compound on endogenous levels of HPA axis hormones.

A total of 8 female subjects, ages 19 to 58, with a medical diagnosis of classical 21-hydroxylase deficiency CAH were administered single bedtime doses (hs) of NBI-77860 300 mg, 600 mg, and placebo during three separate treatment periods (see study design schematic in Figure 4). The subjects’ usual morning dose of concurrent steroidal treatment was delayed until after the 16-hour postdose blood samples were collected (*i.e.*, until approximately 1400h).

The PD endpoints for this study included the HPA axis biomarkers of interest in this patient population; namely, 17-hydroxyprogesterone (17-OHP; as the primary PD endpoint), adrenocorticotrophic hormone (ACTH), androstenedione, testosterone, and serum cortisol levels. The initial analysis of PD variables was an examination of the grouped subject data for each biomarker, expressed as a mean percent change from predose levels for the two active dosing conditions relative to the placebo condition. The data for mean 17-OHP and ACTH levels throughout the 24-hour postdose period are provided in Figure 5.

Consistent and clinically meaningful reductions from predose levels of both 17-OHP and ACTH were observed throughout the postdose period following administration of NBI-77860 relative to placebo in these CAH patients. In addition to the group mean data, individual responses were evaluated and treatment “responders” were conservatively defined as those subjects with at least a 50% decrease in 17-OHP and ACTH under active NBI-77860 relative to placebo during the peak morning period.

This responder analysis yielded a sizeable responder rate of 50% in the study (none of these subjects were responders during the initial placebo treatment period). Furthermore, the 300 mg dose yielded nearly identical effects on 17-OHP and ACTH as the 600 mg dose. An example of an individual subject response for these biomarkers is
5 provided in Figure 6.

The various embodiments described above can be combined to provide further embodiments. All U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications
10 referred to in this specification and/or listed in the Application Data Sheet, including U.S. Provisional Application Serial Nos. 61,929,941, filed January 21, 2014; 61,981,033, filed April 17, 2014; and 62/069,155, filed October 27, 2014, are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and
15 publications to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible
20 embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

I claim the following:

1. A method for treating Congenital Adrenal Hyperplasia (CAH) by administering to a subject in need thereof a CRF₁ receptor antagonist having a dissociation half-life in excess of 30 minutes.
2. The method of claim 1 wherein the CRF₁ receptor antagonist has a dissociation half-life in excess of 40 minutes.
3. The method of claim 1 wherein the CRF₁ receptor antagonist has a dissociation half-life in excess of 50 minutes.
4. The method of claim 1 wherein the CRF₁ receptor antagonist is Compound I (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methoxy)phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine).
5. The method of claim 1 wherein the CRF₁ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-e]pyrimidin-4-amine), or DMP904.
6. The method of any one of claims 1-5 wherein the CRF₁ receptor antagonist is administered at bedtime.
7. The method of any one of claims 1-5 wherein the CRF₁ receptor antagonist is administered at or before the expected circadian release of ACTH.

8. The method of claim 7 wherein the CRF₁ receptor antagonist is administered 3-4 hours before the expected circadian release of ACTH.

9. A method for reducing 17-OHP and ACTH levels in a subject who has Congenital Adrenal Hyperplasia (CAH), said method comprising administering to the subject a CRF₁ receptor antagonist at bedtime.

10. The method of claim 9, wherein the CRF₁ receptor antagonist is administered at or before the expected circadian release of ACTH.

11. The method of claim 9, wherein the CRF₁ receptor antagonist is administered 3-4 hours before the expected circadian release of ACTH.

12. The method of any one of claims 9-11, wherein the CRF₁ receptor antagonist is Compound 1 (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methoxy)phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine).

13. The method of any one of claims 9-11, wherein the CRF₁ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-c]pyrimidin-4-amine), or DMP904.

14. A CRF₁ receptor antagonist for use in treating Congenital Adrenal Hyperplasia (CAH), wherein the CRF₁ receptor antagonist has a dissociation half-life in excess of 30 minutes.

15. The CRF₁ receptor antagonist of claim 14, wherein the CRF₁ receptor antagonist has a dissociation half-life in excess of 40 minutes.

16. The CRF₁ receptor antagonist of claim 14, wherein the CRF₁ receptor antagonist has a dissociation half-life in excess of 50 minutes.

17. The CRF₁ receptor antagonist of claim 14, wherein the CRF₁ receptor antagonist is Compound I (NBI-77860; 2,5-dimethyl-3-[2-methyl-4-(methyloxy)phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]pyrazolo[1,5-a]pyrimidin-7-amine).

18. The CRF₁ receptor antagonist of claim 14, wherein the CRF₁ receptor antagonist is NBI-30775, NBI-34041, SSR-126374, SSR-125543, antalarmin (N-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)pyrrolo[3,2-e]pyrimidin-4-amine), or DMP904.

19. The CRF₁ receptor antagonist of any one of claims 14-18, wherein the CRF₁ receptor antagonist is suitable for administration at bedtime.

20. The CRF₁ receptor antagonist of any one of claims 14-18, wherein the CRF₁ receptor antagonist is suitable for administration at or before the expected circadian release of ACTH.

21. The CRF₁ receptor antagonist of any one of claims 14-18, wherein the CRF₁ receptor antagonist is suitable for administration 3-4 hours before the expected circadian release of ACTH.

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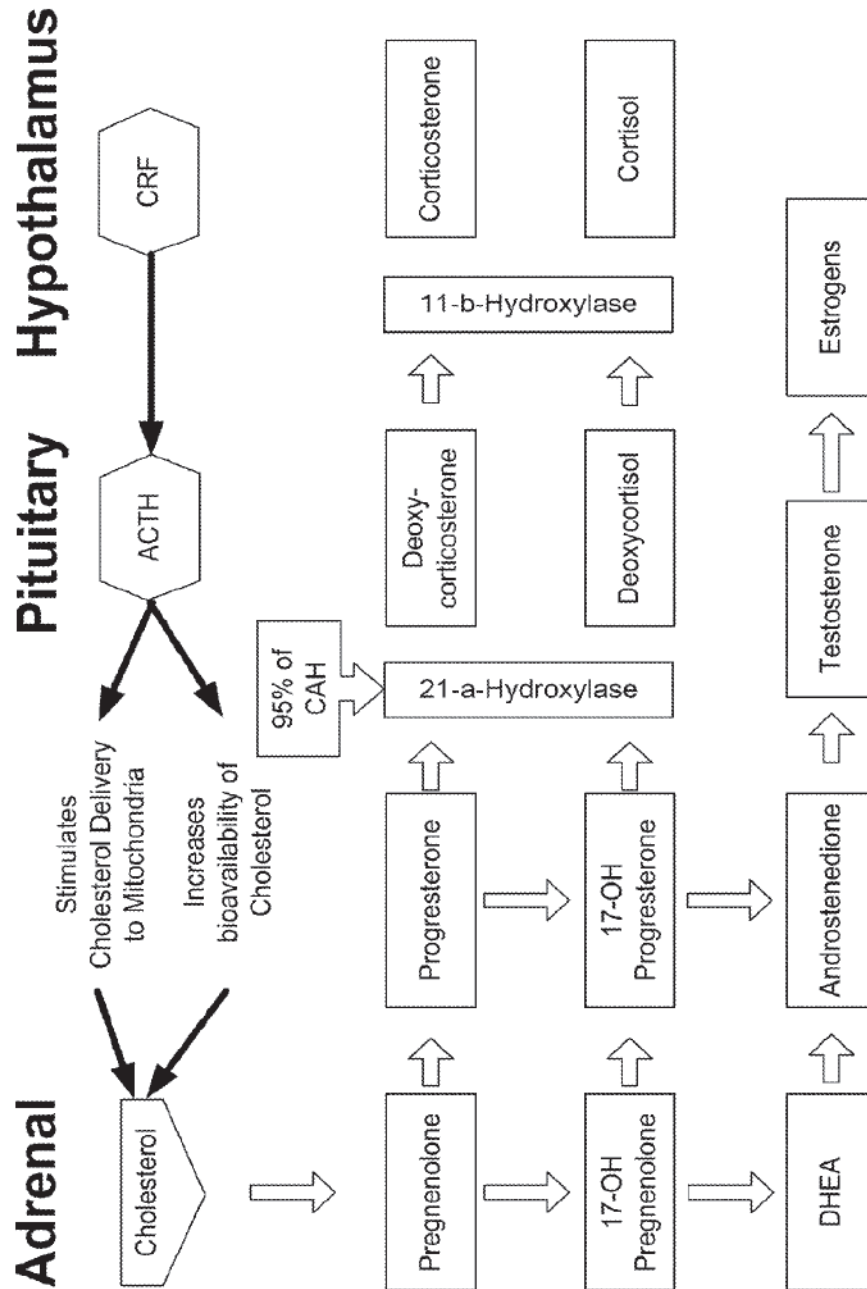


FIG. 1

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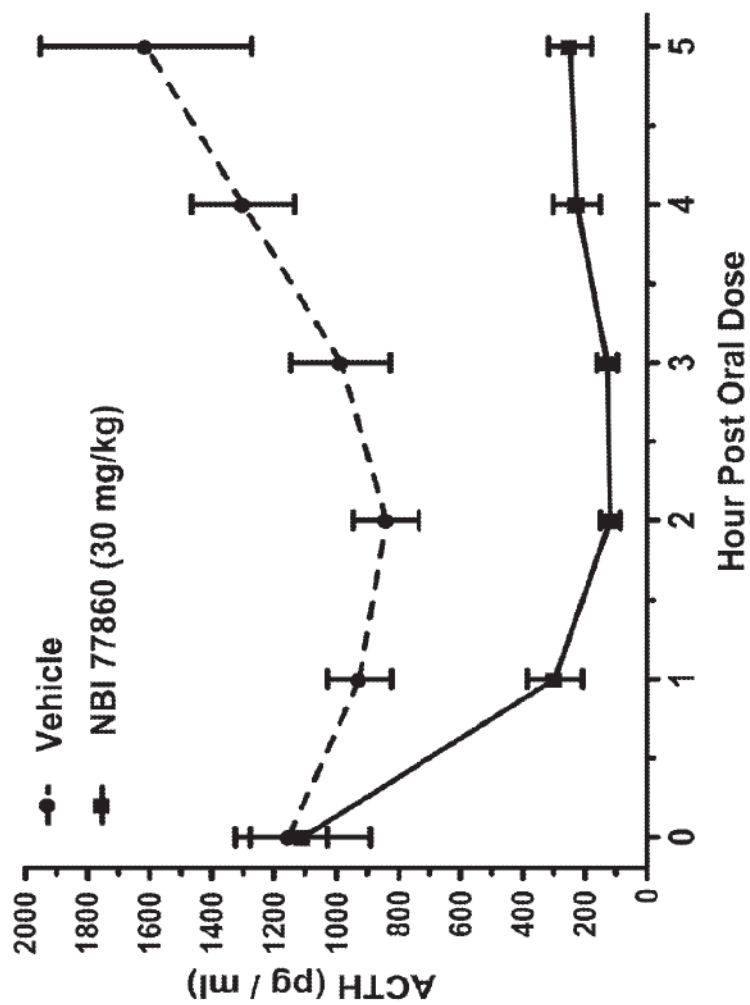
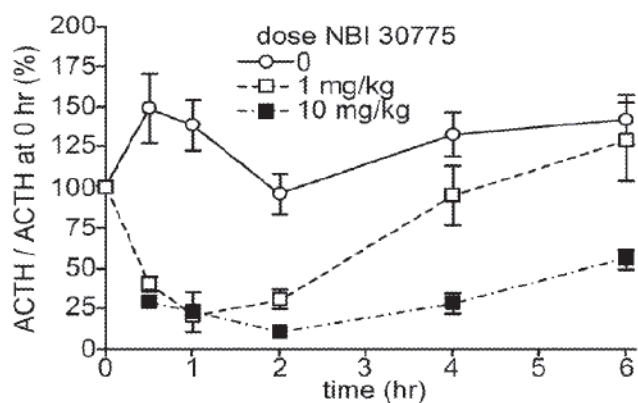
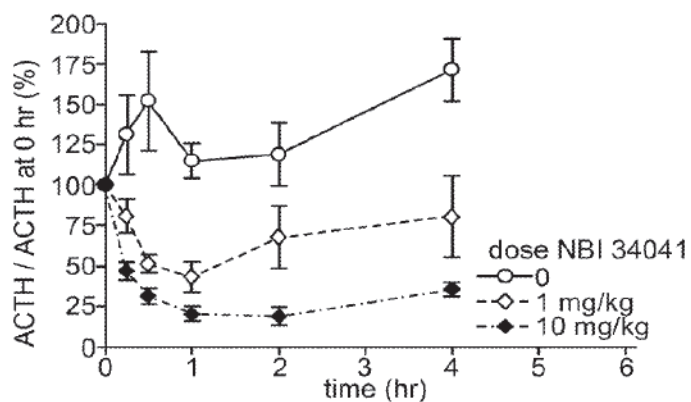
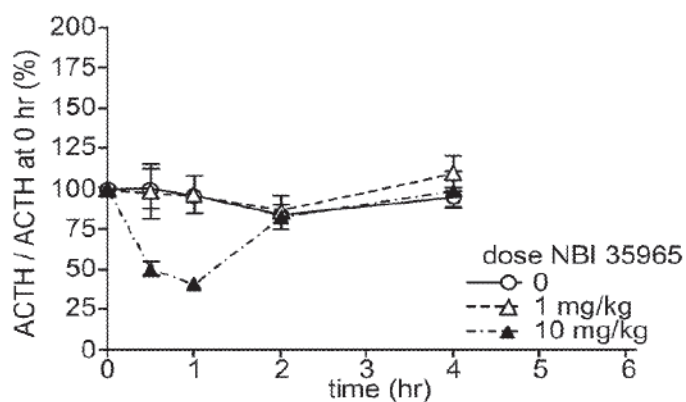


FIG. 2

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**FIG. 3A****FIG. 3B****FIG. 3C**

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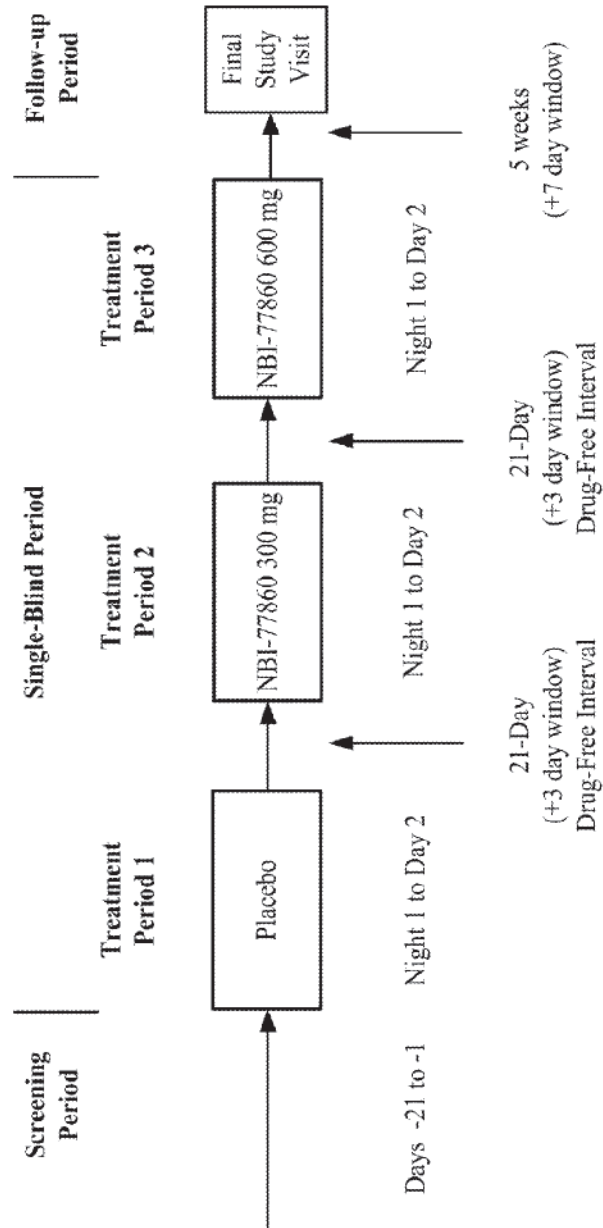
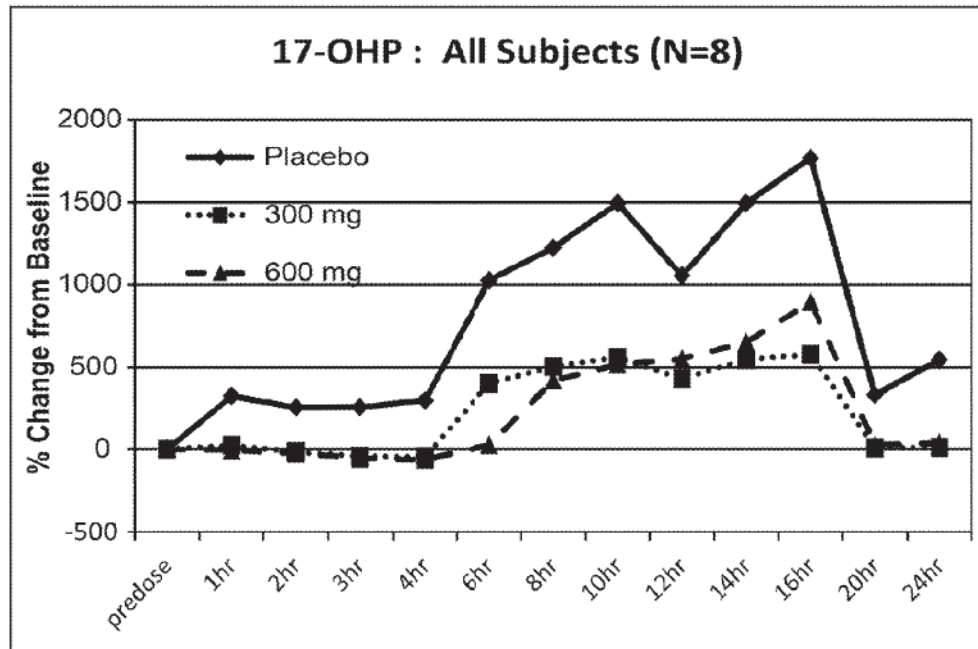
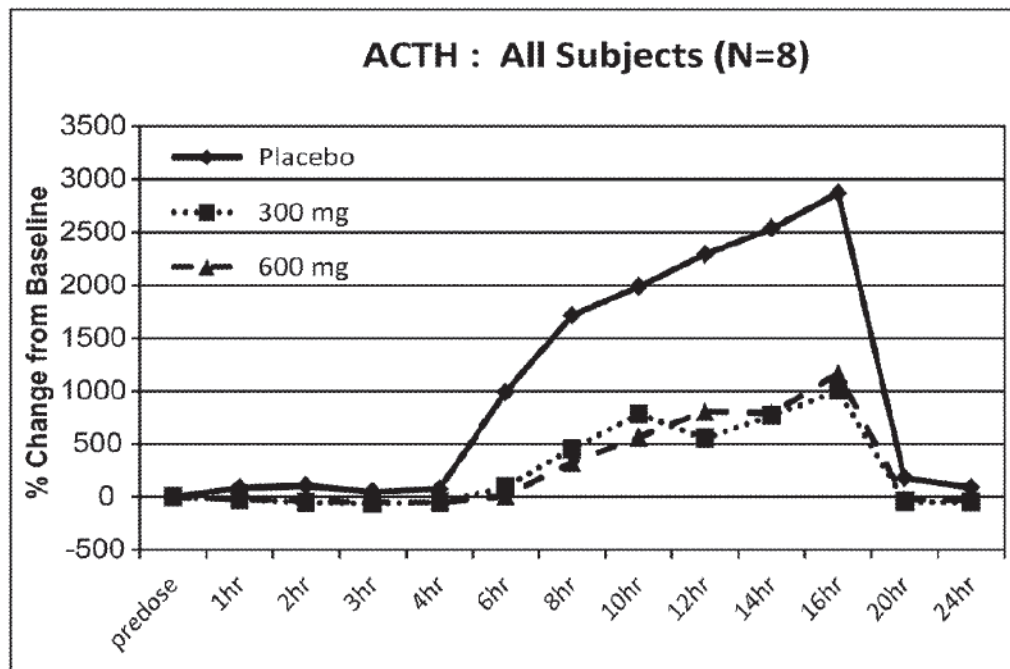


FIG. 4

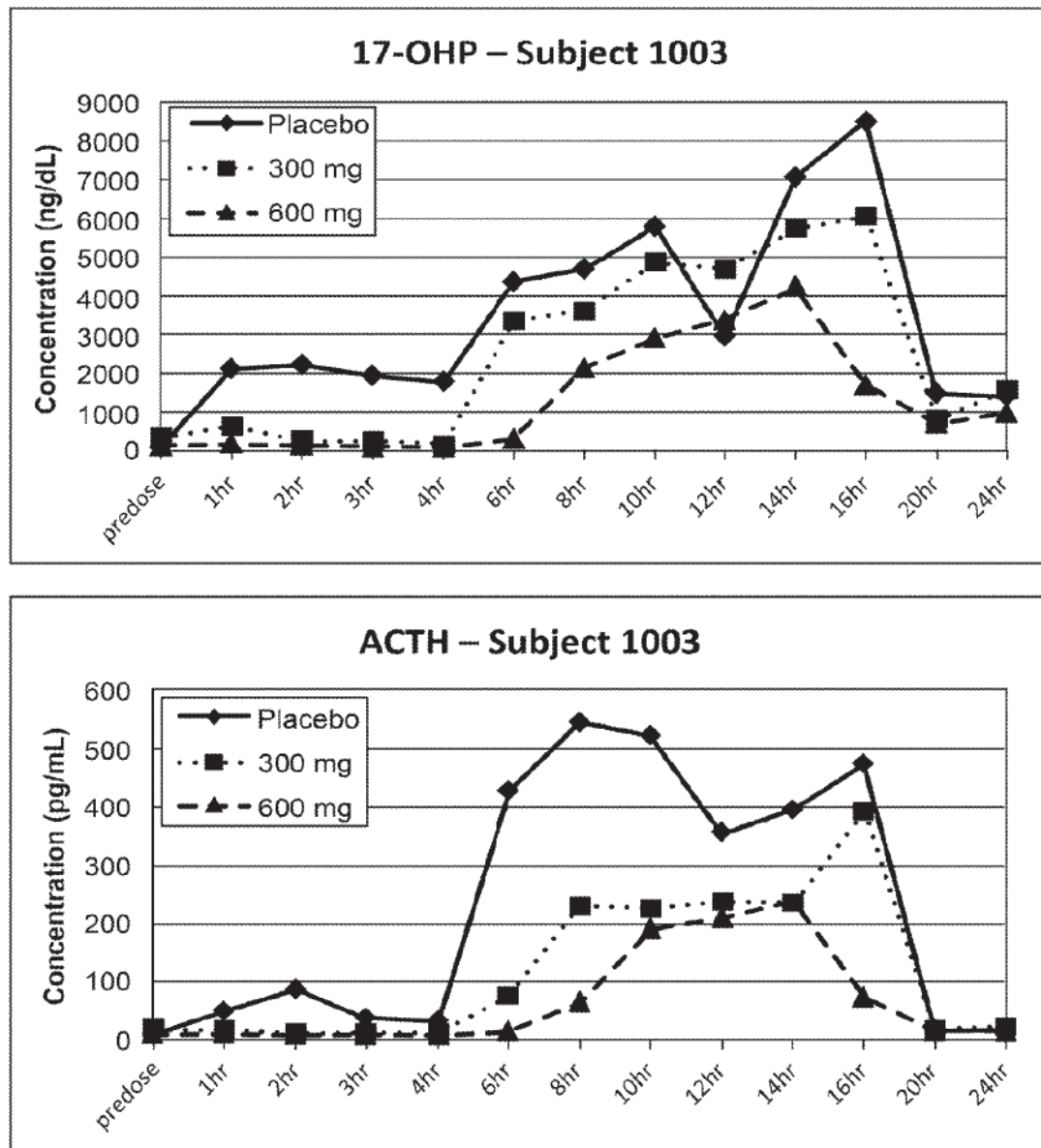
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**FIG. 5**

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**FIG. 6**

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/012315

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/427 A61K31/4985 A61K31/519
ADD.

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

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)

EPO-Internal, EMBASE, BIOSIS

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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Y	column 2, lines 13-46 column 2, line 56	1-21
X	----- ZOUMAKIS E ET AL: "Corticotropin-releasing hormone receptor antagonists", EUROPEAN JOURNAL OF ENDOCRINOLOGY, vol. 155, no. Suppl. 1, November 2006 (2006-11), pages S85-S91, XP002738177, ISSN: 0804-4643	1-3,5, 14-16,18
Y	page S86, left-hand column, paragraph 3; table 1 ----- -/-	1-21



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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Engl, Brigitte

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/012315

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). 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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International application No

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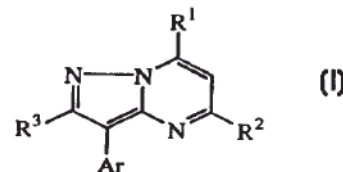
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 487/04, A61K 31/495		A1	(11) International Publication Number: WO 97/29109
			(43) International Publication Date: 14 August 1997 (14.08.97)
(21) International Application Number: PCT/EP97/00459		(74) Agent: WANTE, Dirk; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).	
(22) International Filing Date: 30 January 1997 (30.01.97)			
(30) Priority Data: 60/011,279 7 February 1996 (07.02.96) US 60/027,688 8 October 1996 (08.10.96) US		(81) Designated States: AL, AM, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicants (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). NEUROCRINE BIOSCIENCES INC. [US/US]; 3050 Science Park Road, San Diego, CA 92121-1102 (US).		Published With international search report.	
(72) Inventors; and (75) Inventors/Applicants (for US only): CHEN, Chen [CN/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). WEBB, Thomas, R. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). McCARTHY, James, R. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). MORAN, Terence, J. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). WILCOXEN, Keith, M. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US).			

(54) Title: PYRAZOLOPYRIMIDINES AS CRF RECEPTOR ANTAGONISTS

(57) Abstract

This invention concerns compounds of formula (I), including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein R¹ is NR⁴R⁵ or OR⁵; R² is C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkylthio; R³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfoxy or C₁₋₆alkylthio; R⁴ is hydrogen, C₁₋₆alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, C₃₋₆cycloalkyl, C₃₋₆alkenyl, hydroxyC₁₋₆alkyl, C₁₋₆alkylcarbonyloxyC₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl; R⁵ is C₁₋₆alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, Ar¹CH₂, C₁₋₆alkyloxyC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₃₋₆alkenyl, thienylmethyl, furanymethyl, C₁₋₆alkylthioC₁₋₆alkyl, morpholinyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylC₁₋₆alkyl, C₁₋₆alkyl substituted with imidazolyl; or a radical of the formula -Alk-O-CO-Ar¹; or R⁴ and R⁵ taken together with the nitrogen atom to which they are attached may form an optionally substituted pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group; having CRF receptor antagonistic properties; pharmaceutical compositions containing such compounds as active ingredients; methods of treating disorders related to hypersecretion of CRF such as depression, anxiety, substance abuse, by administering an effective amount of a compound of formula (I).



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PYRAZOLOPYRIMIDINES AS CRF RECEPTOR ANTAGONISTS

Background of the invention

- 5 This invention relates to pyrazolopyrimidines which possess CRF receptor antagonistic properties, to pharmaceutical compositions containing these compounds as active ingredient, and the use thereof in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.
- 10 The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalmi and identified as a 41-amino acid peptide (Vale et al., *Science* 213:1394-1397, 1981). Subsequently, sequences of human and rat CRF were isolated and determined to be identical, but different from ovine CRF in 7 of the 41 amino acid residues (Rivier et al., *Proc. Natl. Acad. Sci. USA* 80:4851, 1983; Shibahara et al., *EMBO J.* 2:775, 1983).
- 15 CRF has been found to produce profound alterations in endocrine, nervous and immune system functions. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotrophic hormone ("ACTH"), β -endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., *Science* 213:1394-1397, 1981). Briefly, CRF is believed to initiate its biological
- 20 effects by binding to a plasma membrane receptor which has been found to be distributed throughout the brain (DeSouza et al., *Science* 221:1449-1451, 1984), pituitary (DeSouza et al., *Methods Enzymol.* 124:560, 1986; Wynn et al., *Biochem. Biophys. Res. Comm.* 110:602-608, 1983), adrenals (Udelsman et al., *Nature* 319:147-150, 1986) and spleen (Webster, E.L., and E.B. DeSouza, *Endocrinology* 122:609-617, 1988). The CRF receptor is coupled to a GTP-binding protein (Perrin et al., *Endocrinology* 118: 1171- 1179, 1986) which mediates CRF-stimulated increase in intracellular production of cAMP (Bilezikjian, L.M., and W.W. Vale, *Endocrinology* 113:657-662, 1983).
- 25
- 30 In addition to its role in stimulating the production of ACTH and POMC, CRF is also believed to coordinate many of the endocrine autonomic, and behavioral responses to stress, and may be involved in the pathophysiology of affective disorders. Moreover, CRF is believed to be a key intermediary in communication between the immune, central nervous, endocrine and cardiovascular systems (Crofford et al., *J. Clin. Invest.* 90:2555-2564, 1992; Sapolsky et al., *Science* 238:522-524, 1987; Tilders et al., *Regul. Peptides* 5:77-84, 1982). Overall, CRF appears to be one of the pivotal central nervous
- 35 system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.

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Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment. For example, intracerebroventricular injection of CRF results in behavioral activation (Sutton et al., *Nature* 297:331, 1982), persistent activation of the electroencephalogram (Ehlers et al., *Brain Res.* 2/8332, 1983), stimulation of the sympathoadrenomedullary pathway (Brown et al., *Endocrinology* 110:928, 1982), an increase of heart rate and blood pressure (Fisher et al., *Endocrinology* 110:2222, 1982), an increase in oxygen consumption (Brown et al., *Life Sciences* 30:207, 1982), alteration of gastrointestinal activity (Williams et al., *Am. J. Physiol.* 253:G582, 1987), suppression of food consumption (Levine et al., *Neuropharmacology* 22:337, 1983), modification of sexual behavior (Sirinathsinghji et al., *Nature* 305:232, 1983), and immune function compromise (Irwin et al., *Am. J. Physiol.* 255:R744, 1988). Furthermore, clinical data suggest that CRF may be hypersecreted in the brain in depression, anxiety-related disorders, and anorexia nervosa. (DeSouza, *Ann. Reports in Med. Chem.* 25:215-223, 1990).

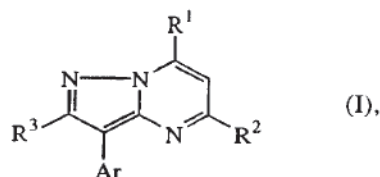
Accordingly, clinical data suggest that CRF receptor antagonists may represent novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

CRF receptor antagonists have been reported in for example, U.S. Patent No. 5,063,245 disclosing substituted 4-thio-5-oxo-3-pyrazoline derivatives and Australian Patent No. AU-A-41399/93, disclosing substituted 2-aminothiazole derivatives. WO-92/18504 and JP-32/04877 disclose pyrazolo[1,5-a]pyrimidines as antiinflammatory agents. Also, WO-94/13676, WO-94/13677 and WO-95/33750 disclose pyrrolopyrimidines, pyrazolo[3,4-d]pyrimidines and substituted purines as CRF receptor antagonists. Arylpyrazolo[1,5-a]pyrimidines have been described as xanthine oxidase inhibitors (Robins et al., *J. Heterocyclic Chem.* 22:601-634, 1985). JP-42/011,753 discloses 7-methylamino-pyrazolo[1,5-a]pyrimidine derivatives useful as sedative and antiphlogistic agents. And JP-61/057,587 discloses pyrazolo[1,5-a]pyrimidine derivatives useful as antiulcer agents.

Due to the physiological significance of CRF, the development of further biologically active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.

Description of the invention

This invention concerns CRF antagonistic compounds of formula (I)



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including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

R¹ is NR⁴R⁵ or OR⁵;

R² is C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkylthio;

10 R³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfoxy or C₁₋₆alkylthio;

R⁴ is hydrogen, C₁₋₆alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, C₃₋₆cycloalkyl, C₃₋₆alkenyl, hydroxyC₁₋₆alkyl, C₁₋₆alkylcarbonyloxyC₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl;

15 R⁵ is C₁₋₈alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, Ar¹CH₂, C₁₋₆alkyloxyC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₃₋₆alkenyl, thienylmethyl, furanylmethyl, C₁₋₆alkylthioC₁₋₆alkyl, morpholinyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylC₁₋₆alkyl, C₁₋₆alkyl substituted with imidazolyl; or a radical of formula -Alk-O-CO-Ar¹;

20 or R⁴ and R⁵ taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl; and

Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C₁₋₆alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆alkyloxy, benzyloxy, C₁₋₆alkylthio, nitro, amino and mono- or di(C₁₋₆alkyl)amino; pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents independently selected from halo, C₁₋₆alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆alkyloxy, benzyloxy, C₁₋₆alkylthio, nitro, amino, mono- or di(C₁₋₆alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;

30 Ar¹ is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, trifluoromethyl and C₁₋₆alkyl substituted with morpholinyl; or pyridinyl; and Alk is C₁₋₆alkanediyl.

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In a further aspect the invention concerns novel compounds of formula (I) as defined above, with the proviso that 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo[1,5-a]-pyrimidine and 2,5-dimethyl-7-(methylamino)-3-phenyl-pyrazolo[1,5-a]pyrimidine are not included

The proviso is intended to exclude compounds disclosed in JP-61/057,587 and JP-42/011,753.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₁₋₆alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof; C₁₋₂alkyl defines straight saturated hydrocarbon radicals having from 1 to 2 carbon atoms such as methyl and ethyl; C₂₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as ethyl, propyl, butyl, 1-methylethyl and the like; C₃₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 3 to 4 carbon atoms such as propyl, butyl, 1-methylethyl and the like; C₁₋₆alkyl includes C₁₋₂alkyl and C₃₋₄alkyl radicals as defined hereinbefore and the higher homologs thereof having from 5 to 6 carbon atoms such as, pentyl, the pentyl isomers, hexyl and the hexyl isomers; C₁₋₈alkyl includes C₁₋₆alkyl and the higher homologues thereof having from 7 to 8 carbon atoms such as, for example, heptyl, octyl and the like; C₃₋₆alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the like; and where said C₃₋₆alkenyl is linked to a nitrogen or oxygen, the carbon atom making the link preferably is saturated. C₃₋₆cycloalkyl comprises cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. HydroxyC₁₋₆alkyl refers to C₁₋₆alkyl substituted with a hydroxyl-group. Homopiperidinyl refers to a 7 membered saturated ring containing one nitrogen atom.

Depending on the nature of some of the substituents, the compounds of formula (I) may contain one or more asymmetric centers which may be designated with the generally used R and S nomenclature.

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- The compounds of the present invention contain basic nitrogen atoms and, as such, can be present as the free base or in the form of acid addition salts, both being part of this invention. Acid addition salts may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids.
- Particular groups of compounds within the invention are those compounds of formula (I) wherein one or more of the following restrictions apply :
- a) R^1 is NR^4R^5 wherein R^4 is hydrogen, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyloxy C_{1-6} alkyl or C_{3-6} alkenyl; in particular C_{2-4} alkyl, hydroxy C_{1-2} alkyl, C_{3-4} alkenyl or C_{1-2} alkylcarbonyloxy C_{2-4} alkyl; and R^5 is C_{1-8} alkyl, C_{3-6} alkenyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, phenylmethyl or C_{3-6} cycloalkylmethyl; in particular C_{2-4} alkyl, C_{3-4} alkenyl, hydroxy C_{2-4} alkyl or cyclopropylmethyl;
 - b) R^1 is OR^5 wherein R^5 is C_{1-6} alkyl; in particular C_{2-4} alkyl;
 - c) R^2 is C_{1-6} alkyl; in particular C_{1-2} alkyl;
 - d) R^3 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylthio; in particular hydrogen, C_{1-2} alkyl or C_{1-2} alkylthio;
 - e) Ar is a phenyl substituted with 1, 2 or 3 substituents each independently selected from C_{1-6} alkyl, C_{1-6} alkyloxy or halo; wherein the phenyl moiety is preferably substituted in the 3-, 4-, 6-, 2,4- or 2,4,6-positions; or Ar is a pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, amino, nitro, trifluoromethyl, mono- or di(C_{1-6} alkyl)amino, piperidinyl or C_{1-6} alkyl; wherein the pyridinyl moiety preferably is connected via the 2- or 3-position to the remainder of the molecule.
- Another particular group of compounds are those compounds of formula (I) wherein R^1 is NR^4R^5 and R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl.
- Preferred compounds are those compounds of formula (I) wherein R^1 is NR^4R^5 and R^4 is C_{3-4} alkyl or allyl, preferably propyl; R^5 is C_{2-4} alkyl, allyl or cyclopropylmethyl, preferably propyl; R^2 is methyl; R^3 is hydrogen, methyl or methylthio, preferably

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propyl; and Ar is a phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, methyl or methoxy; and Ar in particular is pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, methyl or dimethylamino.

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More preferably Ar is 3-pyridinyl substituted in the 4- and/or 6-position with methyl or dimethylamino.

Most preferred are those compounds selected from

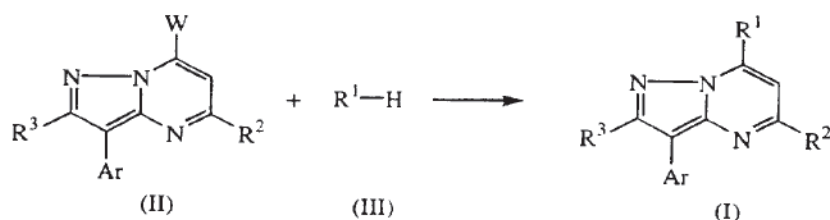
- 10 3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-propyl-*N*-cyclopropanemethylamino)-pyrazolo[2,3-*a*]pyrimidine;
 3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-allyl-*N*-cyclopropanemethylamino)-pyrazolo[2,3-*a*]pyrimidine;
 2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(*N,N*-diallylamino)-
 15 pyrazolo[2,3-*a*]pyrimidine;
 2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-butyl-*N*-cyclopropanemethylamino)pyrazolo[2,3-*a*]pyrimidine;
 2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-propyl-*N*-cyclopropanemethylamino)pyrazolo[2,3-*a*]pyrimidine;
 20 2-methyl-3-(4-chlorophenyl)-5-methyl-7-(*N,N*-dipropylamino)-pyrazolo[2,3-*a*]pyrimidine;
 3-[6-(dimethylamino)-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropylpyrazolo[2,3-*a*]pyrimidin-7-amine; or
 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropyl-
 25 pyrazolo[2,3-*a*]pyrimidine-7-amine; or
 3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(*N*-propyl-*N*-methoxyethylamino)-pyrazolo[2,3-*a*]pyrimidine;
 the stereoisomeric forms and the pharmaceutically acceptable acid addition salts thereof.

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The compounds of the present invention can generally be prepared by alkylating a pyrazolopyrimidine of formula (II) with an intermediate of formula (III). In intermediate (II), W is an appropriate leaving group such as halo, e.g. chloro, bromo, or a sulfonyloxy group, e.g. a mesyloxy or a tosyloxy group.

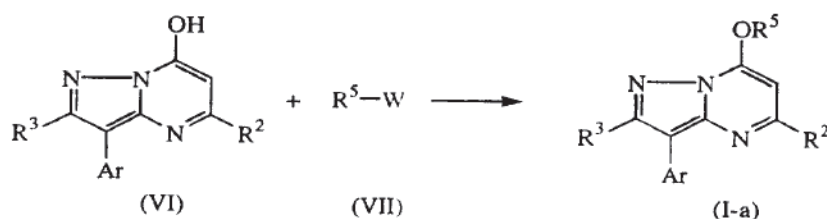
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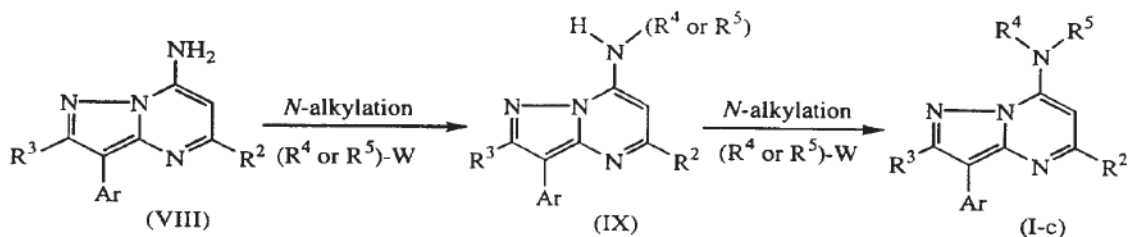
The above reaction is typically conducted in a suitable solvent, e.g. an aprotic solvent such as DMF or acetonitrile, an ether, e.g. tetrahydrofuran, preferably at an elevated temperature and, when the intermediates of formula (III) are volatile amines, in a sealed reaction vial.

Also, compounds of formula (I) wherein R^1 is OR^5 , said compounds being represented by formula (I-a), may be prepared by *O*-alkylating an intermediate of formula (VI) with an intermediate of formula (VII), wherein W is as defined above.



Said reaction for preparing compounds of formula (I-a) can be performed in a reaction-inert solvent such as, for example, *N,N*-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, preferably at a temperature ranging between room temperature and reflux temperature.

The compounds of formula (I) wherein R^1 is NR^4R^5 , represented by formula (I-c), can be prepared from either compounds of formula (VIII) or (IX) by suitable *N*-alkylation reactions as depicted herebelow, wherein W is as previously defined. These *N*-alkylations are conducted in a reaction-inert solvent such as, for example, an ether e.g. tetrahydrofuran and preferably in the presence of a strong base, e.g. NaH.



In certain instances, this reaction can give rise to side products wherein R^2 is alkylated by (R^4 or R^5)-W, in particular where R^2 is methyl and R^4 or R^5 is C_{1-6} alkyl.

5 As outlined below, compounds of formula (I) may be converted into each other following art-known transformation procedures.

10 The compounds of formula (I) wherein R^3 is C_{1-6} alkylthio can be converted into compounds of formula (I) wherein R^3 is C_{1-6} alkylsulfonyl or C_{1-6} alkylsulfoxy by an oxidation reaction, e.g. treatment with a peroxide such as 3-chloroperbenzoic acid in a reaction-inert solvent, e.g. dichloromethane. By controlling the amount of oxidant and other reaction parameters, either compounds of formula (I) wherein R^3 is C_{1-6} alkylsulfonyl or C_{1-6} alkylsulfoxy can be obtained, or a mixture of both, which subsequently can be separated by conventional methods, e.g. column chromatography.

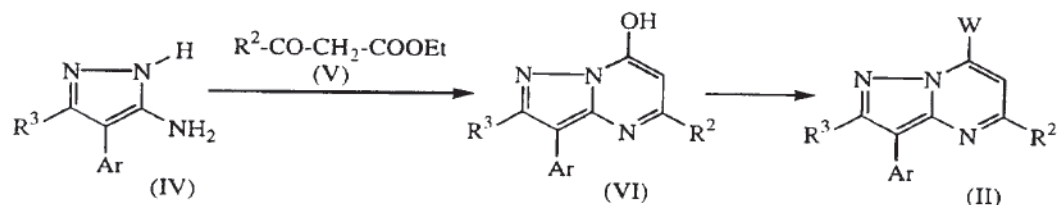
15 The compounds of formula (I) may also be converted into each other via art-known reactions or functional group transformations. For instance, compounds of formula (I) bearing a hydroxy C_{1-6} alkyl group may be converted into compounds of formula (I) bearing a C_{1-6} alkylcarbonyloxy C_{1-6} alkyl group, e.g. by treatment with an acid anhydride in an reaction-inert solvent such as, e.g. dichloromethane, and optionally in
20 the presence of a base such as, e.g. pyridine.

Compounds of formula (I) bearing a nitro group may be converted to compounds of formula (I) bearing an amino group and subsequently to compounds of formula (I) having a mono- or di(C_{1-6} alkyl)amino group. Also, the amino group may be converted
25 using a diazotization reaction to a halo.

Further, the Ar group of compounds of formula (I) can be halogenated using a halogenating agent such as, e.g. chlorine or bromine, in a suitable solvent, e.g. acetic acid, and optionally the reaction may be performed at a temperature ranging between
30 room temperature and the reflux temperature of the reaction mixture.

Intermediates of formula (II) can be prepared according to the procedure as described in Robins et al., *J. Heterocyclic Chem.* 22:601-634, 1985.

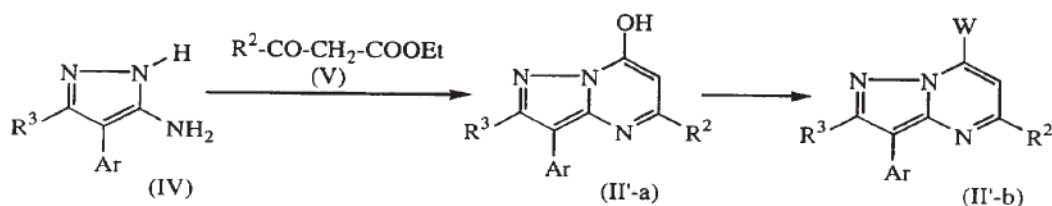
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Aminopyrazole derivatives (IV) are reacted with a β -keto ester (V), preferably under reflux conditions and in a suitable reaction-inert solvent such as an ether, e.g. THF, yielding hydroxypyrazolopyrimidines (VI) which are converted into intermediates of formula (II) by converting the hydroxy group of intermediate (VI) into leaving group W, e.g. by treating (VI) with methanesulfonyloxy chloride or a halogenating reagent such as, e.g. $POCl_3$.

Intermediates of formula (VIII) are prepared by treating intermediates of formula (II) with ammonia.

In an embodiment, this invention also provides for intermediates of formula (II'), wherein W' represents hydroxy, halo, mesyloxy or tosyloxy; with the proviso that Ar is other than phenyl.



Said intermediates of formula (II') may be prepared according to procedures used to prepare intermediates of formula (II), thereby thereby yielding compounds of formula (II'-a), defined as compounds of formula (II') wherein W' is hydroxy; and optionally converting compounds of formula (II'-a) into compounds of formula (II'-b), defined as compounds of formula (II') wherein W' is other than hydroxy.

Stereoisomers may be prepared by separation of the end products of formula (I) following art-known procedures, e.g. by treatment with an optically active acid and separating the thus-formed diastereoisomeric salts by selective crystallization or column chromatography. Or, stereoisomers may be prepared by using stereoisomeric starting materials in any of the above reaction schemes or in the preparation of intermediates described hereinafter.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (*J. Neuroscience* 7:88, 1987) and Battaglia et al. (*Synapse* 1:572, 1987). As mentioned above, suitable CRF antagonists include compounds which demonstrate CRF receptor affinity. CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (e.g. [¹²⁵I]tyrosine CFR) to receptor (e.g., receptors prepared from rat cerebral cortex membranes). The radioligand binding assay described by DeSouza et al. (*supra*, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the IC₅₀ as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a "K_i" value calculated by the following equation :

$$K_i = \frac{IC_{50}}{1 + L / K_D}$$

where L = radioligand and K_D = affinity of radioligand for receptor (Cheng and Prusoff, *Biochem. Pharmacol.* 22:3099, 1973).

In addition to inhibiting CRF receptor binding, a compound's CRF receptor antagonist activity may be established by the ability of the compound to antagonize an activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylate cyclase activity. Therefore, compounds may be evaluated as CRF antagonists by their ability to antagonize CRF-stimulated adenylate cyclase activity by, for example, measuring cAMP levels. The CRF-stimulated adenylate cyclase activity assay described by Battaglia et al. (*supra*, 1987) provides an assay for determining a compound's ability to antagonize CRF activity. Accordingly, CRF receptor antagonist activity may be determined by assay techniques which generally include an initial binding assay (such as disclosed by DeSouza (*supra*, 1987)) followed by a cAMP screening protocol (such as disclosed by Battaglia (*supra*, 1987)). With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a K_i of less than 10 μM. In a preferred embodiment of this invention, a

CRF receptor antagonist has a K_i of less than 1 μM , and more preferably less than 0.25 μM (*i.e.*, 250 nM).

The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurologic disorders or illnesses. More specifically, the CRF receptor antagonists of the present invention may be useful in treating physiological conditions or disorders arising from the hypersecretion of CRF. Because CRF is believed to be a pivotal neurotransmitter that activates and coordinates the endocrine, behavioral and automatic responses to stress, the CRF receptor antagonists of the present invention can be used to treat neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by the CRF receptor antagonists of this invention include affective disorders such as depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, cardiovascular abnormalities such as unstable angina and reactive hypertension; and feeding disorders such as anorexia nervosa, bulimia, and irritable bowel syndrome. CRF antagonists may also be useful in treating stress-induced immune suppression associated with various diseases states, as well as stroke. Other uses of the CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).

In another embodiment of the invention, pharmaceutical compositions containing one or more CRF receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a CRF receptor antagonist of the present invention (*i.e.*, a compound of structure (I)) and a pharmaceutically acceptable carrier and/or diluent. The CRF receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder, that is, in an amount sufficient to achieve CRF receptor antagonist activity, and preferably with acceptable toxicity to the patient. Preferably, the pharmaceutical compositions of the present invention may include a CRF receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a CRF receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the CRF receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, USA, 1990.

In another embodiment, the present invention provides a method for treating a variety of disorders or illnesses, including endocrine, psychiatric and neurologic disorders or illnesses. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the disorder or illness. Such methods include systemic administration of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain, in addition to the CRF receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

As mentioned above, administration of a compound of the present invention can be used to treat a wide variety of disorders or illnesses. In particular, the compounds of the present invention may be administered to a warm-blooded animal for the treatment of depression, anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, unstable angina, reactive hypertension, anorexia nervosa, bulimia, irritable bowel syndrome, stress-induced immune suppression, stroke, inflammation, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

Hence, this invention provides the use of compounds of formula (I) for the manufacture of a medicine for treating physiological conditions or disorders arising from the hypersecretion of corticotropin-releasing factor (CRF); and in a further embodiment the use of novel compounds of formula (I) as a medicine is provided.

The following examples are provided for purposes of illustration, not limitation.

Experimental part

Hereinafter "THF" means tetrahydrofuran and "DCM" means dichloromethane.

A. Preparation of the intermediates.

Example A.1

a) 3-Amino-4-(2,4-dichlorophenyl)pyrazole and ethyl acetoacetate (2 equivalents) were dissolved in dioxane and heated under reflux overnight. The mixture was concentrated *in vacuo* and diluted with ethyl acetate. An off-white solid formed after 2 days standing was collected by vacuum filtration, yielding 3-(2,4-dichlorophenyl)-5-methyl-7-hydroxypyrazolo[2,3-a]pyrimidine (intermediate 1).

b) Intermediate 1 (300 mg) was mixed with POCl₃ (1.5 ml) and heated to reflux for 1 hour. The resultant purple solution was carefully transferred into ice-water. The product was extracted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over MgSO₄ and concentrated *in vacuo* to give 3-(2,4-dichlorophenyl)-5-methyl-7-chloropyrazolo[2,3-a]pyrimidine (intermediate 2) as a brown solid (260 mg, 82%).

Example A.2

a) To a stirred solution of sodium hydride (60%, 25 mmol) in THF (10 ml) 6-(dimethylamino)-3-pyridineacetonitrile was added dropwise (10 mmol) in THF (10 ml). The solution was allowed to stir for 10 minutes before ethyl acetate (30 mmol) was added slowly. The resulting suspension was stirred at room temperature for another hour. The reaction mixture was concentrated under vacuum and dissolved in ethyl acetate/methanol (1:1) and filtered through silica. The filtrate was concentrated, yielding (intermediate 7).

b) A mixture of intermediate 7 and hydrazine hydrobromide (100 mmol) was dissolved in ethanol/water (9:1, total 100 ml) and refluxed for 1 hour. The reaction mixture was concentrated and the residue was partitioned between ethyl acetate and sodium bicarbonate solution. The combined extracts were dried over sodium sulfate, filtered and concentrated to dryness. The residue was dissolved in 1,4-dioxane (200 ml) and

refluxed for 16 hours in the presence of ethyl acetoacetate. The reaction mixture was cooled and an off-white solid precipitated out. Diethyl ether was added to aid in crystallization and the precipitate was filtered off and dried, yielding 3-[2-(dimethylamino)-5-pyridinyl]-2,5-dimethyl-7-hydroxypyrazolo[2,3-a]pyrimidine

5 (intermediate 8).

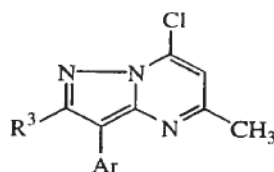
c) Intermediate 8 was dissolved in POCl₃ (2 ml) and refluxed for 2 hours. The reaction mixture was cooled and poured onto ice. The solution was made basic (pH = 9) by addition of solid sodium carbonate and extracted with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated, yielding 3-[6-(dimethylamino)-3-pyridinyl]-2,5-dimethyl-7-chloro-pyrazolo[2,3-a]pyrimidine

10 (intermediate 9).

Table 1 lists the intermediates that were prepared according to one of the above Examples.

15

Table 1 :



Interm. No.	Ex. No.	R ³	Ar
2	A.1	H	2,4-dichlorophenyl
3	A.1	CH ₃ S	2,4-dichlorophenyl
4	A.1	CH ₃	2,4-dichlorophenyl
5	A.1	H	4-chlorophenyl
6	A.1	H	2,6-dichlorophenyl
13	A.1	CH ₃	4-chlorophenyl
14	A.1	CH ₃	3-methoxyphenyl
15	A.1	CH ₃	4-methoxyphenyl
16	A.1	CH ₃	2,4-dimethoxyphenyl
17	A.1	CH ₃ CH ₂	3,4-dimethoxyphenyl
18	A.1	H	2,4,6-trimethoxyphenyl
9	A.2	CH ₃	6-dimethylamino-3-pyridinyl
10	A.2	CH ₃	6-dimethylamino-4-methyl-3-pyridinyl
11	A.2	CH ₃	6-methyl-5-nitro-2-pyridinyl
12	A.2	CH ₃	5-chloro-2-pyridinyl

Interm. No.	Ex. No.	R ³	Ar
19	A.1	CH ₃	6-methyl-3-pyridinyl
20	A.1	CH ₃	3-methyl-5-nitro-2-pyridinyl

B. Preparation of the final products.

Example B.1

- 5 A mixture of intermediate 2 (21 mg) and *N*-propyl-*N*-cyclopropanemethylamine (75 mg) was heated in a sealed reaction vial at 100°C overnight. Chromatography on a preparative TLC plate with 1:5 ethyl acetate-hexanes gave 3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-propyl-*N*-cyclopropanemethylamino)-pyrazolo[2,3-*a*]pyrimidine (compound 17) (17.4 mg) and 3-(2,4-dichlorophenyl)-5-methyl-7-(*N*-cyclopropane-
- 10 methylamino)-pyrazolo[2,3-*a*]pyrimidine (compound 8) (1 mg). In a similar way, starting from intermediate 2 and (S)-(-)-leucinol respectively (R)-(+)-leucinol, (S)-2[[3-(2,4-dichlorophenyl)-5-methyl-7-pyrazolo[2,3-*a*]pyrimidinyl]amino]-4-methyl-1-pentanol (compound 11) and its R-analog (compound 12) were prepared.

15 Example B.2

- A solution of intermediate 10 (8 g) and di-*n*-propylamine (13 g) in acetonitrile (50 ml) was heated at reflux for 3 hours. The mixture was filtrated through a short silica gel plug with ethyl acetate and the filtrate was concentrated *in vacuo* to provide a light yellow solid which was recrystallized from ether-hexanes, yielding 8.9 g (93%) of 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropylpyrazolo[2,3-*a*]-
- 20 pyrimidin-7-amine (compound 53). Compound 53 was also converted to its hydrochloric acid addition salt by dissolving compound 53 (8.1 g) in a mixture of diethyl ether (150 ml) and DCM (50 ml) and treating said mixture with HCl in diethyl ether (1 M, 21.3 ml) dropwise with stirring.
- 25 The resulting off-white solid was collected by filtration, yielding 8.7 g (98%) of 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropylpyrazolo[2,3-*a*]pyrimidin-7-amine monohydrochloride.

Example B.3

- Intermediate 3 (15 mg) was dissolved in ethanol (0.5 ml) and stirred in the presence of
- 30 sodium ethoxide (12 mg) for 1 hour. Chromatography on silica gel gave 3-(2,4-dichlorophenyl)-7-(ethoxy)-5-methyl-2-methylthio-pyrazolo[2,3-*a*]pyrimidine (compound 50).

-16-

Example B.4

A solution of compound 6 (14 mg) in THF (3 ml) was treated with sodium hydride (60 mg, excess) at room temperature for 5 minutes, followed by iodopropane (0.3 ml). The reaction was stirred at room temperature overnight and quenched with methanol (0.5 ml). The resultant mixture was loaded onto a preparative TLC plate and developed with 1:5 ethyl acetate-hexanes to give 3-(2,4-dichlorophenyl)-5-methyl-7-[*N*-(3-methoxypropyl)-*N*-propylamino]-pyrazolo[2,3-*a*]pyrimidine (compound 45) (5.7 mg) as a colorless oil, 3-(2,4-dichlorophenyl)-5-butyl-7-[*N*-(3-methoxypropyl)-*N*-propylamino]-pyrazolo[2,3-*a*]pyrimidine (compound 46) (4 mg) and 3-(2,4-dichlorophenyl)-5-butyl-7-[3-methoxy-propylamino]-pyrazolo[2,3-*a*]pyrimidine (compound 47) (3.5 mg).

Example B.5

Compound 26 (8 mg) was dissolved in DCM (1 ml) and treated with acetic anhydride (0.1 ml) and pyridine (0.1 ml). The mixture was stirred at room temperature overnight and concentrated in vacuo. The residue was diluted with ethyl acetate and filtrated through a short silica gel column. Concentration of the filtrate gave 3-(2,4-dichlorophenyl)-5-methyl-7-[*N*-(2-acetoxyethyl)-*N*-benzylamino]-pyrazolo[2,3-*a*]pyrimidine (compound 27) (8.6 mg) as a colorless oil.

Example B.6

A solution of compound 40 (20 mg) in DCM (3 ml) was treated with 3-chloroperbenzoic acid (19 mg). The solution was stirred at room temperature for 1 hour. Chromatography on a silica gel plate with ethyl acetate-hexanes (1:1) yielded compound 43 and compound 44.

Example B.7

A mixture of compound 55, palladium on activated carbon (100 mg) in dry ethanol (100 ml) was put on the hydrogenation unit and hydrogenation was carried out at 2.7 10⁵ Pa (40 psi) for 2 hours. The reaction mixture was filtered and concentrated. The residue was dissolved in diethyl ether and concentrated, yielding 1.49 g of 3-(5-amino-3-methyl-2-pyridinyl)-2,5-dimethyl-*N,N*-dipropyl-pyrazolo[2,3-*a*]pyrimidine-7-amine (compound 56).

Example B.8

To a stirring solution of compound 56 (1.39 g) and aqueous formaldehyde (6.4 g) in ACN (20 ml) was added sodium cyanoborohydride (743 mg) at 0°C. Glacial acetic

- acid (1 ml) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over sodium sulfate, filtered, concentrated to dryness and purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 150:10:1). The desired fraction was isolated, yielding 1.30 g of 3-[5-(dimethylamino)-3-methyl-2-pyridinyl]-2,5-dimethyl-*N,N*-dipropyl-pyrazolo[2,3-*a*]pyrimidine-7-amine (compound 57).

Example B.9

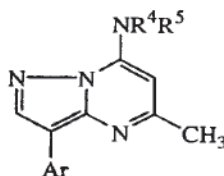
- To a solution of compound 56 (100 mg) in a mixture of concentrated HCl (1 ml) and water (1 ml), cooled in an ice bath, was added a solution of sodium nitrite (21 mg) in water (1 ml). The solution was added to a mixture of copper(I)chloride (281 mg) in concentrated HCl with stirring in an ice bath. A solid separated and the mixture was heated to 60°C and a clear solution was obtained. The reaction mixture was basified with NaOH, extracted with ethyl acetate, washed with brine and concentrated. Purification by preparative TLC yielded 16 mg of compound 98.

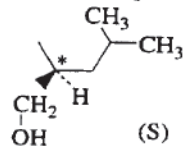
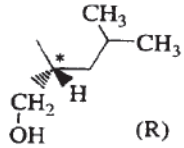
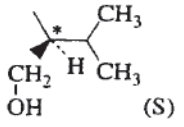
Example B.10

- Compound 56 (100 mg) was added to a solution of fluoroboric acid (48% wt in water, 2 ml), cooled in an ice bath, followed by addition of a solution of sodium nitrite (20 mg) in water (1 ml). The temperature was kept under 10°C. The solid was collected by filtration, dried and partitioned between an aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was washed with brine, concentrated and the residue was purified by preparative TLC yielding 20 mg of compound 100.

Tables 2 to 5 list the compounds that were prepared according to one of the above Examples and tables 6 and 7 list the analytical data for these compounds.

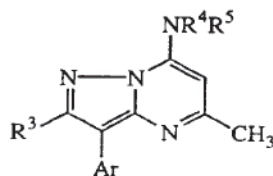
Table 2 :



Co. No.	Ex. No.	R ⁴	R ⁵	Ar
1	B.1	hydrogen	n-propyl	2,4-dichlorophenyl
2	B.1	hydrogen	2-methylpropyl	2,4-dichlorophenyl
3	B.1	hydrogen	1,1-dimethylethyl	2,4-dichlorophenyl
4	B.1	hydrogen	3-hydroxypropyl	2,4-dichlorophenyl
5	B.1	hydrogen	3-pentyl	2,4-dichlorophenyl
6	B.1	hydrogen	CH ₃ O(CH ₂) ₃ -	2,4-dichlorophenyl
7	B.1	hydrogen	(CH ₃) ₂ CHO(CH ₂) ₃ -	2,4-dichlorophenyl
8	B.1	hydrogen	cyclopropylmethyl	2,4-dichlorophenyl
9	B.1	hydrogen	3-methyl-2-butyl	2,4-dichlorophenyl
10	B.1	hydrogen	4-methyl-2-pentyl	2,4-dichlorophenyl
11	B.1	hydrogen		2,4-dichlorophenyl
12	B.1	hydrogen		2,4-dichlorophenyl
13	B.1	hydrogen		2,4-dichlorophenyl
14	B.3	methyl	cyclopropylmethyl	2,4-dichlorophenyl
15	B.1	ethyl	n-butyl	2,4-dichlorophenyl
16	B.2	n-propyl	n-propyl	2,4-dichlorophenyl
17	B.1	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
18	B.1	n-propyl	HOCH ₂ CH ₂ -	2,4-dichlorophenyl
19	B.1	n-propyl	CH ₃ O(CH ₂) ₂ -	2,4-dichlorophenyl
20	B.2	n-propyl	n-propyl	4-chlorophenyl
21	B.1	n-propyl	cyclopropyl	2,6-dichlorophenyl
22	B.1	n-propyl	CH ₃ O(CH ₂) ₂	2,6-dichlorophenyl
23	B.4	n-butyl	cyclopropylmethyl	2,4-dichlorophenyl
24	B.1	2-methylpropyl	cyclopropylmethyl	2,4-dichlorophenyl
25	B.1	3-methyl-2-butyl	cyclopropylmethyl	2,4-dichlorophenyl

Co. No.	Ex. No.	R ⁴	R ⁵	Ar
26	B.1	HOCH ₂ CH ₂ -	phenylmethyl	2,4-dichlorophenyl
27	B.5	CH ₃ COO(CH ₂) ₂ -	phenylmethyl	2,4-dichlorophenyl
28	B.5	CH ₃ COO(CH ₂) ₂ -	n-propyl	2,4-dichlorophenyl
29	B.4	allyl	cyclopropylmethyl	2,4-dichlorophenyl
45	B.4	n-propyl	CH ₃ O(CH ₂) ₃	2,4-dichlorophenyl
58	B.1	CH ₃ O(CH ₂) ₂ -	CH ₃ O(CH ₂) ₂ -	2,4-dichlorophenyl
59	B.1	hydrogen	CH ₃ OCH ₂ CH(CH ₃)-	2,4-dichlorophenyl
60	B.1	hydrogen	1-hydroxy-2-hexyl	2,4-dichlorophenyl
61	B.1	hydrogen	1-hydroxy-2-pentyl	2,4-dichlorophenyl
62	B.2	n-propyl	n-propyl	6-dimethylamino-2,4-dimethyl-3-pyridinyl
63	B.1	ethyl	n-butyl	6-dimethylamino-2,4-dimethyl-3-pyridinyl
64	B.1	n-propyl	cyclopropylmethyl	6-dimethylamino-2,4-dimethyl-3-pyridinyl
65	B.1	n-propyl	cyclopropylmethyl	6-methyl-3-pyridinyl
66	B.1	n-butyl	n-butyl	6-methyl-3-pyridinyl
67	B.1	n-propyl	cyclopropylmethyl	2,4-dimethoxyphenyl
68	B.2	n-propyl	n-propyl	2,4,6-trimethoxyphenyl
69	B.1	n-propyl	CH ₃ O(CH ₂) ₂ -	2,4,6-trimethoxyphenyl
70	B.1	n-propyl	cyclopropylmethyl	2,4,6-trimethoxyphenyl
71	B.1	ethyl	n-butyl	2,4,6-trimethoxyphenyl
72	B.1	ethyl	ethyl	2,4,6-trimethoxyphenyl

Table 3 :

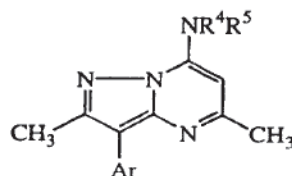


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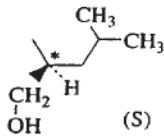
Co. No.	Ex. No.	R ³	R ⁴	R ⁵	Ar
30	B.1	CH ₃ S	hydrogen	n-propyl	2,4-dichlorophenyl
31	B.1	CH ₃ S	hydrogen	2-propyl	2,4-dichlorophenyl

Co. No.	Ex. No.	R ³	R ⁴	R ⁵	Ar
32	B.1	CH ₃ S	hydrogen	3-heptyl	2,4-dichlorophenyl
34	B.1	CH ₃ S	hydrogen	2-methoxyphenylmethyl	2,4-dichlorophenyl
35	B.1	CH ₃ S	methyl	methyl	2,4-dichlorophenyl
36	B.1	CH ₃ S	ethyl	ethyl	2,4-dichlorophenyl
37	B.2	CH ₃ S	n-propyl	n-propyl	2,4-dichlorophenyl
38	B.1	CH ₃ S	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
39	B.1	CH ₃ S	2-propyl	2-propyl	2,4-dichlorophenyl
40	B.1	CH ₃ S	n-butyl	n-butyl	2,4-dichlorophenyl
41	B.1	CH ₃ S	n-butyl	cyclopropylmethyl	2,4-dichlorophenyl
42	B.1	CH ₃ S	allyl	allyl	2,4-dichlorophenyl
43	B.6	CH ₃ SO	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
44	B.6	CH ₃ SO ₂	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
73	B.2	CH ₃ CH ₂	n-propyl	n-propyl	3,4-dimethoxyphenyl

Table 4 :



Co. No.	Ex. No.	R ⁴	R ⁵	Ar
48	B.2	n-propyl	n-propyl	4-chlorophenyl
49	B.1	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
51	B.1	n-propyl	CH ₃ O(CH ₂) ₂ -	2,4-dimethoxyphenyl
52	B.2	n-propyl	n-propyl	6-dimethylamino-3-pyridinyl
53	B.2	n-propyl	n-propyl	6-dimethylamino-4-methyl-3-pyridinyl
54	B.2	n-propyl	n-propyl	5-chloro-2-pyridinyl
55	B.2	n-propyl	n-propyl	3-methyl-5-nitro-2-pyridinyl
56	B.7	n-propyl	n-propyl	5-amino-3-methyl-2-pyridinyl
57	B.8	n-propyl	n-propyl	5-dimethylamino-3-methyl-2-pyridinyl
74	B.1	CH ₃ O(CH ₂) ₂ -	CH ₃ O(CH ₂) ₂ -	4-chlorophenyl
75	B.1	HOCH ₂ CH ₂ -	phenylmethyl	4-chlorophenyl

Co. No.	Ex. No.	R ⁴	R ⁵	Ar
76	B.1	hydrogen	1-hydroxy-2-hexyl	4-chlorophenyl
77	B.1	hydrogen	1-hydroxy-2-pentyl	4-chlorophenyl
78	B.1	hydrogen	CH ₃ S(CH ₂) ₂ -	4-chlorophenyl
79	B.1	hydrogen	 (S)	4-chlorophenyl
80	B.1	hydrogen	1-hydroxy-2-hexyl	6-dimethylamino-4-methyl-3-pyridinyl
81	B.1	ethyl	n-butyl	6-dimethylamino-4-methyl-3-pyridinyl
82	B.1	n-propyl	cyclopropylmethyl	6-dimethylamino-4-methyl-3-pyridinyl
83	B.1	n-propyl	phenylmethyl	6-dimethylamino-4-methyl-3-pyridinyl
84	B.1	allyl	allyl	6-dimethylamino-4-methyl-3-pyridinyl
85	B.1	n-butyl	n-butyl	6-dimethylamino-4-methyl-3-pyridinyl
86	B.1	hydrogen	3-pentyl	6-dimethylamino-4-methyl-3-pyridinyl
87	B.1	hydrogen	2-propyl	6-dimethylamino-4-methyl-3-pyridinyl
88	B.1	hydrogen	4-methyl-2-pentyl	6-dimethylamino-4-methyl-3-pyridinyl
89	B.1	methyl	n-butyl	6-dimethylamino-4-methyl-3-pyridinyl
90	B.2	n-propyl	n-propyl	6-dimethylamino-2-methyl-3-pyridinyl
91	B.1	n-propyl	cyclopropylmethyl	6-dimethylamino-2-methyl-3-pyridinyl
92	B.1	ethyl	n-butyl	6-dimethylamino-2-methyl-3-pyridinyl
93	B.1	n-butyl	n-butyl	6-dimethylamino-2-methyl-3-pyridinyl
94	B.1	n-propyl	n-propyl	4,6-dimethyl-3-pyridinyl
95	B.1	n-propyl	cyclopropylmethyl	4,6-dimethyl-3-pyridinyl
96	B.2	n-propyl	n-propyl	6-dimethylamino-2,4-dimethyl-3-pyridinyl
97	B.1	n-propyl	cyclopropylmethyl	6-dimethylamino-2,4-dimethyl-3-pyridinyl

Co. No.	Ex. No.	R ⁴	R ⁵	Ar
98	B.9	n-propyl	n-propyl	5-chloro-3-methyl-2-pyridinyl
99	B.9	n-propyl	n-propyl	5-iodo-3-methyl-2-pyridinyl
100	B.10	n-propyl	n-propyl	5-fluoro-3-methyl-2-pyridinyl
101	B.2	n-propyl	n-propyl	3-chloro-5-trifluoromethyl-2-pyridinyl
102	B.1	CH ₃ O(CH ₂) ₂ -	CH ₃ O(CH ₂) ₂ -	3-chloro-5-trifluoromethyl-2-pyridinyl
103	B.2	n-propyl	n-propyl	3,5-dichloro-2-pyridinyl
104	B.1	n-propyl	CH ₃ O(CH ₂) ₂ -	3,5-dichloro-2-pyridinyl
105	B.1	n-propyl	cyclopropylmethyl	3,5-dichloro-2-pyridinyl
106	B.2	n-propyl	n-propyl	3-methyl-5-methoxy-2-pyridinyl
107	B.8	n-propyl	n-propyl	5-diethylamino-3-methyl-2-pyridinyl
33	B.8	n-propyl	n-propyl	6-diethylamino-4-methyl-3-pyridinyl
108	B.8	n-propyl	n-propyl	5-N-piperidinyl-3-methyl-2-pyridinyl
109	B.2	n-propyl	n-propyl	5-methyl-3-nitro-2-pyridinyl
110	B.2	n-propyl	n-propyl	3-amino-5-methyl-2-pyridinyl
111	B.9	n-propyl	n-propyl	3-chloro-5-methyl-2-pyridinyl
112	B.2	n-propyl	n-propyl	3-methylamino-5-methyl-2-pyridinyl
113	B.2	n-propyl	n-propyl	3-dimethylamino-5-methyl-2-pyridinyl
114	B.2	n-propyl	n-propyl	2-methyl-5-pyridinyl
115	B.1	n-propyl	cyclopropylmethyl	4-isopropylphenyl
116	B.2	n-propyl	n-propyl	3,4-dimethoxyphenyl
117	B.1	n-propyl	CH ₃ O(CH ₂) ₂ -	3,4-dimethoxyphenyl
118	B.1	n-propyl	cyclopropyl	2,4-dimethoxyphenyl
119	B.1	hydrogen	CH ₃ O(CH ₂) ₂ -	2,4-dimethoxyphenyl
120	B.1	n-propyl	HO(CH ₂) ₂ -	2,4-dimethoxyphenyl
121	B.8	n-propyl	n-propyl	5-methylamino-3-methyl-2-pyridinyl
122	B.2	n-propyl	n-propyl	2,4-dimethoxyphenyl
123	B.1	ethyl	n-butyl	2,4-dimethoxyphenyl
124	B.1	n-propyl	2-hydroxypropyl	2,4-dimethoxyphenyl
125	B.2	n-propyl	n-propyl	4-methoxyphenyl
126	B.2	n-propyl	n-propyl	3-methoxyphenyl
127	B.1	n-propyl	cyclopropylmethyl	3-methoxyphenyl

-23-

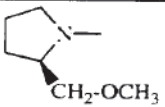
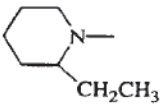
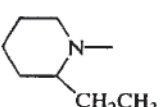
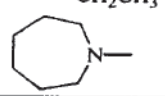
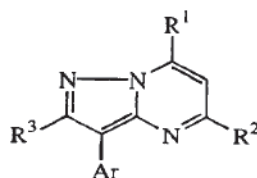
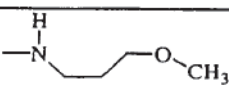
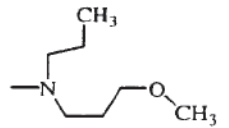
Co. No.	Ex. No.	R ⁴ and R ⁵ taken together	Ar
128	B.1		4-chlorophenyl
129	B.1		4-chlorophenyl
130	B.1		6-dimethylamino-4-methyl-3-pyridinyl
131	B.1		6-dimethylamino-4-methyl-3-pyridinyl

Table 5 :



Co. No.	Ex. No.	R ¹	R ²	R ³	Ar
46	B.4		n-C ₄ H ₉	H	2,4-dichlorophenyl
47	B.4		n-C ₄ H ₉	H	2,4-dichlorophenyl
50	B.3	CH ₃ CH ₂ O-	CH ₃	CH ₃ -S-	2,4-dichlorophenyl

5

Table 6 : Analytical data

Co. No.	¹ H NMR data (CDCl ₃)	MS M + 1
1	δ 0.45 (m,2H), 0.78 (m,2H), 1.20 (m,1H), 2.84 (s,3H), 3.40 (d,2H), 5.98 (s,1H), 7.41 (dd,1H), 7.52 (d,1H), 7.76 (d,1H), 8.32 (s,1H)	335
2	δ 0.88 (d,3H), 1.05 (d,3H), 1.74 (m,1H), 2.52 (s,3H), 3.20 (t,2H), 5.87 (s,1H), 6.40 (t,1H), 7.30 (dd,1H), 7.47 (d,1H), 7.99 (d,1H), 8.42 (s,1H)	349

Co. No.	¹ H NMR data (CDCl ₃)	MS M + 1
3	δ 1.57 (s,9H), 2.54 (s,3H), 6.05 (s,1H), 6.48 (s,1H), 7.31 (d,1H), 7.47 (s,1H), 7.99 (d,1H), 8.39 (s,1H)	349
4	δ 1.97 (m,2H), 2.43 (s,3H), 3.62 (m,2H), 3.75 (t,3H), 4.00 (brs, 1H), 6.18 (s,1H), 7.39 (dd,1H), 7.52 (d,1H), 8.19 (d,1H), 8.43 (s,1H)	351
5	δ 1.03 (t,6H), 1.60-1.85 (m,4H), 2.56 (s,3H), 3.49 (m,1H), 5.92 (s,1H), 6.19 (d,1H), 7.35 (dd,1H), 7.50 (dd,1H), 8.01 (d,1H), 8.44 (s,1H)	363
6	δ 2.02 (m,2H), 2.51 (s,3H), 3.40 (s,3H), 3.51 (m,4H), 5.91 (s,1H), 6.71 (t,1H), 7.31 (dd,1H), 7.47 (d,1H), 7.99 (d,1H), 8.42 (s,1H)	365
7	δ 1.23 (d,6H), 2.00 (m,2H), 2.52 (s,1H), 3.51 (dd,2H), 3.59 (m,2H), 5.90 (s,1H), 6.92 (t,1H), 7.31 (dd, 1H), 7.46 (d,1H), 8.00 (d,1H), 8.41 (s,1H)	393
8	δ 0.35 (m,2H), 0.68 (m,2H), 1.25 (m,1H), 2.52 (s,3H), 3.23 (dd,2H), 5.88 (s,1H), 6.40 (t,1H), 7.32 (d,1H), 7.48 (s,1H), 7.99 (s,1H), 8.43 (s,1H)	347
9	δ 1.03 (d,3H), 1.06 (d,3H), 1.31 (d,3H), 1.95 (m,1H), 2.52 (s,3H), 3.54 (m,1H), 5.88 (s,1H), 6.23 (d,1H), 7.32 (d,1H), 7.47 (s,1H), 7.98 (d,1H), 8.41 (s,1H)	363
10	δ 0.95 (d,3H), 0.97 (d,3H), 1.40-1.80 (m,3H), 2.53 (s,3H), 3.76 (m,1H), 5.89 (s,1H), 6.12 (d,1H), 7.32 (d,1H), 7.47 (s,1H), 7.97 (d,1H), 8.40 (s,1H)	377
11	δ 0.94 (d,3H), 0.99 (d,3H), 1.53 (m,1H), 1.76 (m,1H), 2.50 (s,3H), 2.93 (brs,1H), 3.48 (m,1H), 3.76 (m,1H), 5.97 (s,1H), 6.22 (d,1H), 7.35 (dd, 1H), 7.51 (d,1H), 7.95 (d,1H), 8.36 (s,	393
12	δ 0.92 (d,3H), 0.97 (d,3H), 1.52 (m,2H), 1.72 (m,1H), 2.47 (s,3H), 3.02 (brs,1H), 3.42 (m,1H), 3.72 (m,2H), 5.94 (s,1H), 6.20 (d,1H), 7.33 (d,1H), 7.49 (s,1H), 7.92 (d,1H), 8.33 (s,	393
13	δ 0.99 (d,6H), 1.98 (m,1H), 2.44 (s,3H), 3.22 (brs, 1H), 3.46 (m,2H), 3.73 (m,1H), 5.88 (s,1H), 6.31 (d,1H), 7.32 (d,1H), 7.48 (s,1H), 7.92 (d,1H), 8.32 (s, 1H)	379
14	δ 0.21 (m,2H), 0.54 (m,2H), 1.10 (m,1H), 2.53 (s,3H), 3.28 (s,3H), 3.91 (d,2H), 5.99 (s,1H), 7.32 (d,1H), 7.48 (s,1H), 7.97 (d,1H), 8.43 (s,1H)	379

Co. No.	¹ H NMR data (CDCl ₃)	MS M + 1
15	δ 0.96 (t,3H), 1.31 (t,3H), 1.38 (m,2H), 1.71 (m,2H), 2.49 (s,3H), 3.74 (t,2H), 3.65 (q,2H), 5.90 (s,1H), 7.30 (dd,1H), 7.46 (d,1H), 7.97 (d,1H), 8.40 (s,1H)	377
16	δ 0.96 (t,6H), 1.73 (m,4H), 2.49 (s,3H), 3.73 (t,4H), 5.88 (s,1H), 7.33 (dd,1H), 7.46 (d,1H), 7.98 (d,1H), 8.40 (s,1H)	377
17	δ 0.26 (m,2H), 0.58 (m,2H), 0.98 (t,3H), 1.18 (m,1H), 1.76 (m,2H), 2.53 (s,3H), 3.76 (d,2H), 3.81 (t,2H), 6.02 (s,1H), 7.34 (dd,1H), 7.49 (dd,1H), 8.44 (s,1H)	389
18	δ 1.04 (t,3H), 1.77 (m,2H), 2.53 (s,3H), 3.47 (t,2H), 3.98 (m,2H), 4.06 (m,2H), 5.52 (brs, 1H), 6.03 (s,1H), 7.33 (d,1H), 7.48 (s,1H), 7.93 (d, 1H), 8.39 (s, 1H)	379
19	δ 0.98 (t,3H), 1.76 (m,2H), 2.50 (s,3H), 3.35 (s,3H), 3.67 (t,2H), 3.72 (m,2H), 4.14 (m,2H), 5.95 (s,3H), 7.29 (d,1H), 7.47 (s,1H), 7.97 (d,1H), 8.39 (s,1H)	393
20	δ 0.96 (t,6H), 1.73 (m,4H), 2.55 (s,3H), 3.74 (t,4H), 5.90 (s,1H), 7.40 (d,2H), 8.04 (d,2H), 8.25 (s,1H)	343
21	δ 0.26 (m,2H), 0.51 (m,2H), 0.92 (t,3H), 1.10 (m,1H), 1.69 (m,2H), 2.72 (s,3H), 3.41 (d,2H), 3.47 (t,2H), 6.17 (s,1H), 7.18 (t,1H), 7.43 (d,2H), 7.99 (s,1H)	389
22	δ 0.93 (t,3H), 1.67 (m,2H), 2.71 (s,3H), 3.32 (s,3H), 3.44 (t,2H), 3.61 (m,2H), 3.68 (m,2H), 6.16 (s,1H), 7.17 (t,1H), 7.41 (d,2H), 7.99 (s,1H)	393
23	δ 0.24 (m,2H), 0.55 (m,2H), 0.95 (t,3H), 1.38 (m,2H), 1.69 (m,2H), 2.51 (s,3H), 3.74 (d,2H), 3.82 (t,2H), 6.00 (s,1H), 7.31 (dd,1H), 7.48 (dd,1H), 7.98 (d,1H), 8.42 (s,1H)	403
24	δ 0.28 (m,2H), 0.50 (m,2H), 0.94 (d,6H), 1.10 (m,1H), 2.05 (m,1H), 2.52 (s,3H), 3.62 (d,2H), 3.82 (d,2H), 6.03 (s,1H), 7.32 (d,1H), 7.47 (s,1H), 7.99 (d,1H), 8.43 (s,1H)	403
25	δ 0.17 (m,2H), 0.47 (m,2H), 0.97 (t,6H), 1.05 (m,1H), 1.67 (m,4H), 2.52 (s,3H), 2.43 (d,2H), 4.71 (m,1H), 6.13 (s,1H), 7.32 (dd,1H), 7.47 (d,1H), 8.02 (d,1H), 8.43 (s,1H)	417
26	δ 2.41 (s,3H), 4.01 (m,2H), 4.15 (m,2H), 4.79 (s,2H), 5.62 (brs, 1H), 6.02 (s,1H), 7.35 (m,6H), 7.48 (s,1H), 7.91 (d,1H), 8.41 (s,1H)	427
27	δ 1.91 (s,3H), 2.47 (s,3H), 4.20 (t,2H), 4.43 (t,2H), 4.96 (s,2H), 6.03 (s,1H), 7.34 (m,6H), 7.49 (s,1H), 7.94 (d,1H), 8.44 (s,1H)	469

28	δ 0.98 (t,3H), 1.74 (m,2H), 1.93 (s,3H), 2.49 (s,3H), 3.59 (m,2H), 4.84 (m,2H), 4.39 (m,2H), 5.95 (s,1H), 7.30 (dd,1H), 7.46 (d,1H), 7.92 (d,1H), 8.38 (s,1H)	421
29	δ 0.28 (m,2H), 0.60 (m,2H), 1.20 (m,1H), 2.51 (s,3H), 3.70 (d,2H), 4.50 (d,2H), 5.29 (d,1H), 5.30 (d,1H), 5.96 (m,1H), 6.05 (s,1H), 7.32 (dd,1H), 7.48 (d,1H), 7.96 (d,1H), 8.44 (s,1H)	387
30	δ 1.07 (t,3H), 1.80 (m,2H), 2.46 (s,3H), 2.55 (s,3H), 3.36 (dt,2H), 5.82 (s,1H), 6.29 (t,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	381
31	δ 1.41 (d,6H), 2.46 (s,3H), 2.55 (s,3H), 3.85 (m,1H), 5.82 (s,1H), 6.08 (d,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	381
32	δ 0.92 (t,3H), 1.01 (t,3H), 1.25-1.80 (m,8H), 2.45 (s,3H), 2.54 (s,3H), 3.48 (m,1H), 5.79 (s,1H), 6.02 (d,1H), 7.27 (d,1H), 7.39 (d,1H), 7.50 (s,1H)	437
33	δ 0.96 (t,3H), 1.20 (t,6H), 1.74 (m, 4H), 2.15 (s,3H), 2.34 (s,3H), 2.41 (s, 3H), 3.56 (t,4H), 3.79 (t,4H), 5.77 (s,1H), 6.41 (s,1H), 7.54 (s,1H)	-
34	δ 2.45 (s,3H), 2.56 (s,3H), 3.93 (s,3H), 4.60 (d,2H), 5.90 (s,1H), 6.70 (t,1H), 6.99 (t,2H), 7.27-7.41 (m,4H), 7.52 (s,1H)	459
35	δ 2.44 (s,3H), 2.60 (s,3H), 3.35 (s,6H), 5.00 (brs,1H), 5.84 (s,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	367
36	δ 1.36 (s,6H), 2.42 (s,3H), 2.59 (s,3H), 3.80 (m,4H), 5.80 (s,1H), 7.29 (d,1H), 7.38 (d,1H), 7.51 (s,1H)	395
37	δ 0.98 (t,6H), 1.78 (m,4H), 2.40 (s,3H), 2.59 (s,3H), 3.69 (m,4H), 5.74 (s,1H), 7.28 (d,1H), 7.48 (d,1H)	423
38	δ 0.30 (m,2H), 0.62 (m,2H), 0.99 (t,3H), 1.20 (m,1H), 1.81 (m,2H), 2.49 (s,3H), 2.59 (s,3H), 3.65-3.90 (m,4H), 5.87 (s,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	435
39	δ 1.05 (d,3H), 1.38 (d,3H), 2.45 (s,3H), 2.56 (s,3H), 3.40 (m,1H), 5.80 (s,1H), 7.30 (d,1H), 7.37 (d,1H), 7.51 (s,1H)	423
40	δ 0.98 (t,6H), 1.40 (m,4H), 1.75 (m,4H), 2.42 (s,3H), 2.59 (s,3H), 3.71 (m,4H), 5.76 (s,1H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	451
41	δ 0.29 (m,2H), 0.61 (m,2H), 0.93 (t,3H), 1.20-1.56 (m,3H), 1.75 (m,2H), 2.43 (s,3H), 2.59 (s,3H), 3.65-3.90 (m,4H), 5.88 (s,1H), 7.30 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	449
42	δ 2.42 (s,3H), 2.59 (s,3H), 4.34 (d,4H), 5.30 (m,4H), 5.87 (s,1H), 6.05 (m,2H), 7.29 (d,1H), 7.39 (d,1H), 7.51 (s,1H)	419

Co. No.	¹ H NMR data (CDCl ₃)	MS M + 1
43	δ 0.31 (m,2H), 0.62 (m,2H), 1.00 (t,3H), 1.23 (m,1H), 1.81 (m,1H), 2.49 (s,3H), 3.05 (brs,3H), 3.42-3.95 (m,4H), 6.04 (s,1H), 7.33 (d,1H), 7.50 (s,1H), 7.51 (d,1H)	451
44	δ 0.13 (m,2H), 0.48 (m,2H), 0.90 (t,3H), 1.05 (m,1H), 1.60 (m,2H), 2.64 (s,3H), 3.05 (brs,3H), 3.48 (d,2H), 3.71 (m,2H), 6.04 (s,1H), 7.37 (d,1H), 7.54 (s,1H), 7.60 (d,1H)	485 (+H ₂ O)
45	δ 0.95 (t,3H), 1.42 (m,2H), 1.98 (m,2H), 2.49 (s,3H), 3.33 (s,3H), 3.56 (m,2H), 3.75 (m,2H), 5.93 (m,1H), 7.31 (d,1H), 7.46 (s,1H), 7.96 (d,1H), 8.40 (s,1H)	407
46	δ 0.91 (t,3H), 0.95 (t,3H), 1.35-2.05 (m,8H), 2.70 (t,2H), 3.33 (s,3H), 3.40 (m,6H), 5.92 (s,1H), 7.30 (d,1H), 7.46 (s,1H), 8.02 (d,1H), 8.41 (s,1H)	449
47	δ 0.87 (t,3H), 1.25 (m,2H), 1.70 (m,2H), 2.04 (m,2H), 2.68 (m,2H), 3.41 (s,3H), 3.56 (m,4H), 5.86 (s,1H), 6.60 (t,1H), 7.31 (d,1H), 7.46 (s,1H), 8.14 (d,1H), 8.50 (s,1H)	407
48	δ 0.95 (t,6H), 1.71 (m,4H), 2.47 (s,3H), 2.55 (s,3H), 3.71 (t,4H), 5.82 (s,1H), 7.39 (d,2H), 7.70 (d,2H)	357
49	δ 0.24 (m,2H), 0.54 (m,2H), 0.96 (t,3H), 1.12 (m,1H), 1.74 (m,2H), 2.35 (s,3H), 2.44 (s,3H), 3.73 (d,2H), 3.76 (t,2H), 5.93 (s,1H), 7.29 (d,1H), 7.35 (d,1H), 7.51 (s,1H)	403
50	δ 1.64 (t,3H), 2.52 (s,3H), 2.60 (s,3H), 4.56 (q,2H), 6.02 (s,3H), 7.30 (d,1H), 7.37 (d,1H), 7.51 (s,1H)	368
52	δ 0.9 (t, 6H), 1.68 (m, 4H), 2.13 (s, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.05 (s, 6H), 3.65 (m, 4H), 5.74 (s, 1H), 6.44 (s, 1H), 8.01 (s, 1H)	M ⁺ = 366
53	δ 0.9 (t, 6H), 1.70 (m, 4H), 2.35 (s, 3H), 2.45 (s, 3H), 3.05 (s, 6H), 3.65 (m, 4H), 5.74 (s, 1H), 6.44 (s, 1H), 8.01 (s, 1H)	M ⁺ = 380
54	δ 0.95 (t, 6H), 1.73 (m, 4H), 2.52 (s, 3H), 2.76 (s, 3H), 3.73 (t, 4H), 5.85 (s, 1H), 7.68 (dd, 1H), 8.45 (d, 1H), 8.57 (d, 1H)	-
55	δ 0.96 (t, 6H), 1.70 - 1.78 (m, 4H), 2.44 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 3.73 (t, 4H), 5.48 (s, 1H), 8.36 (d, 1H), 9.32 (d, 1H)	383
56	δ 0.93 (t, 6H), 1.66 - 1.73 (m, 4H), 2.19 (s, 3H), 2.36 (s, 3H), 2.42 (s, 3H), 3.71 (t, 4H), 5.79 (s, 1H), 6.39 (d, 1H), 8.05 (d, 1H)	353
57	δ 0.96 (t, 6H), 1.62 - 1.70 (m, 4H), 2.2 (s, 3H), 2.36 (s, 3H), 2.40 (s, 3H), 2.96 (s, 6H), 3.68 (t, 4H), 5.76 (s, 1H), 6.91 (d, 1H), 8.08 (d,1H)	381

Table 7 : Analytical data

Co. No.	Mass spectral data	Co. No.	Mass spectral data
58	409 [M ⁺]	95	364 [MH ⁺]
59	365 [M ⁺]	96	395 [MH ⁺]
60	394 [MH ⁺]	97	407 [MH ⁺]
61	380 [MH ⁺]	98	372 [MH ⁺] (Cl ³⁵)
62	381 [MH ⁺]	99	464 [MH ⁺]
63	381 [MH ⁺]	100	356 [MH ⁺]
64	393 [MH ⁺]	101	426 [MH ⁺] (Cl ³⁵)
65	350 [MH ⁺]	102	458 [MH ⁺] (Cl ³⁵)
66	366 [MH ⁺]	103	392 [MH ⁺] (Cl ³⁵)
67	381 [MH ⁺]	104	408 [MH ⁺] (Cl ³⁵)
68	399 [MH ⁺]	105	404 [MH ⁺] (Cl ³⁵)
69	415 [MH ⁺]	106	368 [MH ⁺]
70	411 [MH ⁺]	107	409 [MH ⁺]
71	399 [MH ⁺]	108	421 [MH ⁺]
72	371 [MH ⁺]	109	383 [MH ⁺]
73	397 [MH ⁺]	110	353 [MH ⁺]
74	388 [M ⁺]	111	372 [MH ⁺] (Cl ³⁵)
75	407 [MH ⁺]	112	366 [MH ⁺]
76	373 [MH ⁺]	113	381 [MH ⁺]
77	359 [MH ⁺]	114	338 [MH ⁺]
78	346 [M ⁺]	115	377 [MH ⁺]
79	373 [MH ⁺]	116	383 [MH ⁺]
80	397 [MH ⁺]	117	399 [MH ⁺]
81	381 [MH ⁺]	118	395 [MH ⁺]
82	393 [MH ⁺]	119	415 [MH ⁺]
83	429 [MH ⁺]	120	385 [MH ⁺]
84	377 [MH ⁺]	121	367 [MH ⁺]
85	409 [MH ⁺]	122	383 [MH ⁺]
86	367 [MH ⁺]	123	383 [MH ⁺]
87	339 [MH ⁺]	124	399 [MH ⁺]
88	381 [MH ⁺]	125	338 [MH ⁺]
89	367 [MH ⁺]	126	353 [MH ⁺]
90	381 [MH ⁺]	127	365 [MH ⁺]
91	393 [MH ⁺]	128	370 [M ⁺]

Co. No.	Mass spectral data	Co. No.	Mass spectral data
92	381 [MH ⁺]	129	368 [M ⁺]
93	409 [MH ⁺]	130	393 [MH ⁺]
94	352 [MH ⁺]	131	379 [MH ⁺]

C. Pharmacological examples

Example C.1

REPRESENTATIVE COMPOUNDS HAVING CRF RECEPTOR BINDING

5 ACTIVITY

Compounds were evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by DeSouza et al. (*J. Neurosci.* 7:88-100, 1987). By utilizing various 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 was performed in 1.5 ml Eppendorf tubes using approximately 1×10^6 cells per tube stably transfected with human CRF receptors.

15 Each tube received about 0.1 ml of assay buffer (*e.g.*, Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 20 μ M bacitracin) with or without unlabeled sauvagine, urotensin I or CRF (final concentration, 1 μ M) to determine nonspecific binding, 0.1 ml of [¹²⁵I] tyrosine - ovine CRF (final concentration ~200 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 ml of a membrane suspension of cells containing the CRF receptor. The mixture was incubated for 2 hours at 22°C followed by the separation of the bound and free radioligand by centrifugation. Following two washes of the pellets, the tubes were cut just above the pellet and monitored in a gamma counter for radioactivity at approximately 80% efficiency. All radioligand binding data was analyzed using a non-linear least-square curve-fitting program.

25 Binding activity corresponds to the concentration (nM) of the compound necessary to displace 50% of the radiolabeled ligand from the receptor. The following compounds have a $K_i \leq 250$ nM : 5, 10, 12, 15 - 17, 19, 23, 24, 26, 27, 29, 31 - 33, 36 - 43, 48, 49, 51 - 54 and 57 - 130 as listed in Tables 2 - 5. Compounds 17, 29, 38, 41, 42, 48, 49, 51 - 54, 57, 58, 70, 71, 81 - 85, 90 - 92, 101, 103 - 105, 115, 118, 121 - 123 and 125 were found to show the best score in this test.

Example C.2CRF 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
- 5 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
- 10 volume of 0.5 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 24-well plates and incubated for 1 hour 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, the medium is
- 15 aspirated, the wells rinsed once gently with fresh medium, and the medium aspirated. To determine the amount of intracellular cAMP, 300 µl of a solution of 95% ethanol and 20 mM aqueous hydrochloric acid is added to each well and the resulting suspensions are incubated at -20°C for 16 to 18 hours. The solution is removed into 1.5 ml Eppendorf tubes and the wells washed with an additional 200 µl of ethanol/aqueous
- 20 hydrochloric acid and pooled with the first fraction. The samples are lyophilized and then resuspended with 500 µl sodium acetate buffer. The measurement of cAMP in the samples is performed using a single antibody kit. For the functional assessment of the compounds, a single concentration of CRF or related peptides causing 80% stimulation of cAMP production is incubated along with various concentrations of competing
- 25 compounds (10^{-12} to 10^{-6} M).

Example C.3

- The plus-maze and defensive withdrawal paradigms are correlated measures of exploratory activity sensitive to anxiogenic and anxiolytic effects of experimental
- 30 treatments. These animal models are employed to examine anxiolytic and anti-stress actions of compounds of the present invention.

Example C.3-a : The Elevated Plus-Maze Paradigm

- This test predicts how animals respond to an approach-avoidance situation involving a
- 35 bright lighted space versus a dark "safe" area. Both spaces are elevated off the ground and constitute two runways intersecting in the form of plus sign. This type of

approach-avoidance situation is a classical test of "emotionality" and reactivity and is very sensitive to treatments that produce disinhibition (such as sedative/hypnotic drugs) and stress. No motivational constraints are necessary and the animal is free to remain in the dark or venture out on the open arms. The plus-maze apparatus has four arms (10 x 50 cm) at right angles to each other and is elevated from the floor (50 cm). Two of the arms are enclosed with walls (40 cm high) and two arms have no walls (open arms). Subjects are placed individually onto the center of the maze and allowed free access to all four arms for 5 minutes. Subjects are observed through a window in the door and via an on-line display of the rat's location on a computer monitor. Time spent in each arm is recorded automatically by photocell beams and a computer program. The maze is wiped clean with a damp cloth between each trial. The measure of anxiogenic-like behavior in this task is a decrease in time spent on open arms while the measure of anti-stress efficacy is a complementary increase in time spent on open arms.

15 Validation of the Plus-Maze Using CRF Peptides :

Central administration of CRF and exposure to any of several experimental stressors suppresses exploration in the elevated plus maze model of anxiety. When measuring the behavioral response to social defeat, central administration of the alpha-helical CRF (9-41) antagonist either post-stress [25 µg ICV] or pre-stress [1 µg ICV] reverses the anxiogenic effect of social defeat. This anti-stress action of the CRF antagonist is also exerted following intracerebral administration into the central nucleus of amygdala [250 ng IC].

Rats were administered the test compounds orally one hour prior to the five minute test. Some groups were placed in a water-filled pool for ninety seconds immediately prior to placement on the Plus-Maze (Stress group) while control subjects were removed directly from the home cage (Non-Stress group). In the non-treated animal group a significant reduction of the percentage of the average time spent in the open arms was observed (from about 36 to about 16 %). Upon administration of 2.5 or 20 mg/kg of compound 53, the % time in the open arms returned to a level equal, within the error range, to the untreated group.

Example C.3-b : The defensive Withdrawal Paradigm

Testing takes place in a plexiglas open field (106 x 92 x 77 cm) containing a cylindrical galvanized steel chamber measuring 17.1 cm deep and 10.2 cm in diameter. The chamber is open at one end and is located along the wall of the open field aligned

- lengthwise and 15.0 cm away from a corner of the open field. The open end faces the corner. The open field is illuminated by fluorescent ceiling lighting. For testing, the animals are introduced into the unfamiliar test environment by placing them into the small chamber. Tests take 5 minutes in duration and the apparatus is cleaned with a mild acetic acid solution after each test. The test compound is administered orally one hour before the 5 minutes test. The behavior of the animals is monitored and recorded by video camera. The latency to leave the chamber will be measured and defined as the placement of all four paws in the open field. Also measured is the number of passages made between the chamber and the open field and the average length of time in the chamber per entry. The measure of anxiolytic efficacy is a decrease in mean time spent within the enclosed chamber. Compound 53 reduced the mean time in the chamber from about 80 seconds to about 20 to 40 seconds when administered at doses of 0.63, 2.5 and 20 mg/kg p.o. to rats.
- 15 Validation of Defensive Withdrawal using CRF peptides
- When injected ICV, both alpha-helical CFR (9-41) and CRF modify behavior in the defensive withdrawal paradigm. In particular, ICV administration of CRF in animals previously familiarized with the apparatus increases both the latency to emerge from the small chamber and mean time spent in the chamber over the fifteen minute session.
- 20 Similarly, infusion of CRF into the locus ceruleus produced similar changes in defensive withdrawal behavior suggesting that the interaction of CRF with noradrenergic neurons is involved in defensive withdrawal behavior in rats. Conversely, ICV administration of alpha-helical CRF (9-14) or d-Phe CRF (12-41), competitive CRF receptor antagonists, reverses the CRF-like effect of a restraint
- 25 stressor in familiar environment condition and significantly decreases latency to emerge and mean time in chamber measures in animals unfamiliar with the apparatus.

D. Composition examples

- The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.
- 30 "Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable acid or base addition salt or a stereochemically isomeric form thereof.
- 35

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Example D.1 : Oral solutions

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is
5 combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml).
10 The resulting solution is filled in suitable containers.

Example D.2 : Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The
15 resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I..

Example D.3 : Film-coated tabletsPreparation of tablet core

20 A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole is mixed well and compressed into tablets,
25 giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is
30 molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating
35 apparatus.

Example D.4 : Injectable solution

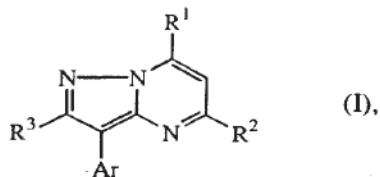
- 1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution
5 was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg/ml of A.I. The solution was sterilized by filtration and filled in sterile containers.

Example D.5 : Suppositories

- 10 3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 Grams surfactant and 300 grams triglycerides were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37 to 38°C to form 100 suppositories each containing 30 mg/ml of the A.I.

Claims

1. A compound of formula



- 5 including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein
- R^1 is NR^4R^5 or OR^5 ;
- R^2 is C_{1-6} alkyl, C_{1-6} alkyloxy or C_{1-6} alkylthio;
- R^3 is hydrogen, C_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfoxy or C_{1-6} alkylthio;
- 10 R^4 is hydrogen, C_{1-6} alkyl, mono- or di(C_{3-6} cycloalkyl)methyl, C_{3-6} cycloalkyl, C_{3-6} alkenyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyloxy C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl;
- R^5 is C_{1-8} alkyl, mono- or di(C_{3-6} cycloalkyl)methyl, Ar^1CH_2 , C_{3-6} alkenyl, C_{1-6} alkyloxy C_{1-6} alkyl, hydroxy C_{1-6} alkyl, thienylmethyl, furanymethyl,
- 15 C_{1-6} alkylthio C_{1-6} alkyl, morpholinyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, di(C_{1-6} alkyl)amino, C_{1-6} alkylcarbonyl C_{1-6} alkyl, C_{1-6} alkyl substituted with imidazolyl; or a radical of formula $-Alk-O-CO-Ar^1$;
- or R^4 and R^5 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group,
- 20 optionally substituted with C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl; and
- Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C_{1-6} alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6} alkyloxy, benzyloxy, C_{1-6} alkylthio, nitro, amino and mono- or di(C_{1-6} alkyl)amino; pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents independently
- 25 selected from halo, C_{1-6} alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6} alkyloxy, benzyloxy, C_{1-6} alkylthio, nitro, amino, mono- or di(C_{1-6} alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;
- Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently
- 30 selected from halo, C_{1-6} alkyl, C_{1-6} alkyloxy, di(C_{1-6} alkyl)amino C_{1-6} alkyl, trifluoromethyl and C_{1-6} alkyl substituted with morpholinyl; or pyridinyl; and
- Alk is C_{1-6} alkanediyl;

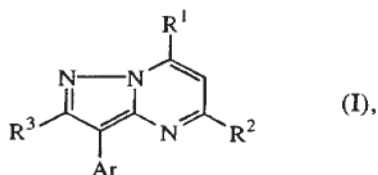
with the proviso that 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo[1,5-a]-pyrimidine and 2,5-dimethyl-7-(methylamino)-3-phenyl-pyrazolo[1,5-a]pyrimidine are not included.

- 5 2. A compound according to claim 1 wherein R¹ is OR⁵ and R⁵ is C₁₋₆alkyl; or R¹ is NR⁴R⁵ and R⁴ is hydrogen, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkylcarbonyloxy-C₁₋₆alkyl or C₃₋₆alkenyl, R⁵ is C₁₋₈alkyl, C₃₋₆alkenyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, phenylmethyl or C₃₋₆cycloalkylmethyl; or R⁴ and R⁵ are
 10 taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl; R² is C₁₋₆alkyl; R³ is hydrogen, C₁₋₆alkyl or C₁₋₆alkylthio; and Ar is a phenyl substituted with 1, 2 or 3
 15 substituents each independently selected from halo, C₁₋₆alkyl or C₁₋₆alkyloxy; or Ar is a pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, amino, nitro, trifluoromethyl, mono- or di(C₁₋₆alkyl)amino, piperidinyl or C₁₋₆alkyl.
- 20 3. A compound according to any of claims 1 to 2 wherein R¹ is NR⁴R⁵ and R⁴ is C₂₋₄alkyl, hydroxyC₁₋₂alkyl, C₃₋₄alkenyl or C₁₋₂alkylcarbonyloxyC₂₋₄alkyl; R⁵ is C₂₋₄alkyl, C₃₋₄alkenyl, hydroxyC₂₋₄alkyl or cyclopropylmethyl; R² is C₁₋₂alkyl; R³ is hydrogen, C₁₋₂alkyl or C₁₋₂alkylthio.
- 25 4. A compound according to any of claims 1 to 3 wherein R¹ is NR⁴R⁵ and R⁴ is C₃₋₄alkyl or allyl; R⁵ is C₂₋₄alkyl, allyl or cyclopropylmethyl; R² is methyl; R³ is methyl; and Ar is phenyl substituted in the 3-, 4-, 6-, 2,4- or 2,4,6-positions with halo, C₁₋₆alkyl or C₁₋₆alkyloxy.
- 30 5. A compound according to any of claims 1 to 3 wherein R¹ is NR⁴R⁵ and R⁴ is C₃₋₄alkyl or allyl; R⁵ is C₃₋₄alkyl, allyl or cyclopropylmethyl; R² is methyl; R³ is methyl; and Ar is 3-pyridinyl substituted on the 4- and/or 6-position with methyl or dimethylamino.
- 35 6. A compound according to claim 1 wherein the compound is 3-[6-(dimethylamino)-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropylpyrazolo[2,3-a]pyrimidin-7-amine, or 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-*N,N*-dipropylpyrazolo[2,3-a]pyrimidin-7-amine;

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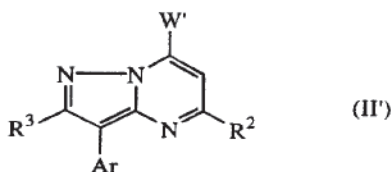
the stereochemically isomeric forms, or the pharmaceutically acceptable acid addition salts thereof.

7. A composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 6.
8. A process for preparing a composition as claimed in claim 7 characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 6 is intimately mixed with a pharmaceutically acceptable carrier.
9. A compound according to any one of claims 1 to 6 for use as a medicine.
10. The use of compounds of formula

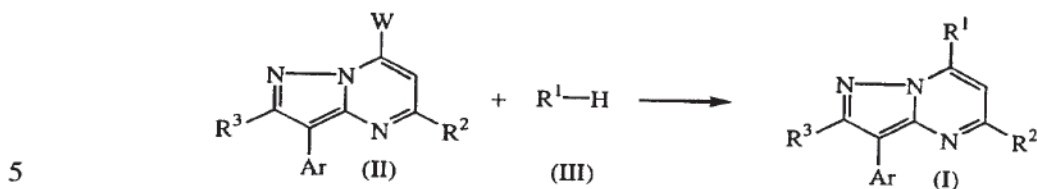


including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein R¹, R², R³ and Ar are as defined in claim 1, including the compounds 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo[1,5-a]pyrimidine and 2,5-dimethyl-7-(methylamino)-3-phenyl-pyrazolo[1,5-a]pyrimidine, for the manufacture of a medicament for treating physiological conditions or disorders arising from the hypersecretion of corticotropin-releasing factor (CRF).

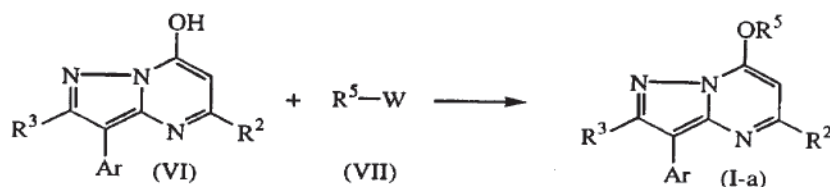
11. A compound of formula (II') wherein the radicals R², R³ and Ar are as defined in any of claims 1 to 5 and radical W' is hydroxy, halo, mesyloxy or tosyloxy; a stereoisomeric form or an acid addition salt form thereof, with the proviso that compounds wherein Ar is unsubstituted phenyl are not included.



12. A process of preparing a compound as claimed in claim 1, characterized by
a) reacting an intermediate of formula (II) with an intermediate of formula (III) in a reaction-inert solvent,



- b) *O*-alkylating an intermediate of formula (VI) with an intermediate of formula (VII) in a reaction-inert solvent and in the presence of a suitable base, yielding compounds of formula (I-a), defined as compounds of formula (I) wherein R¹ is OR⁵.

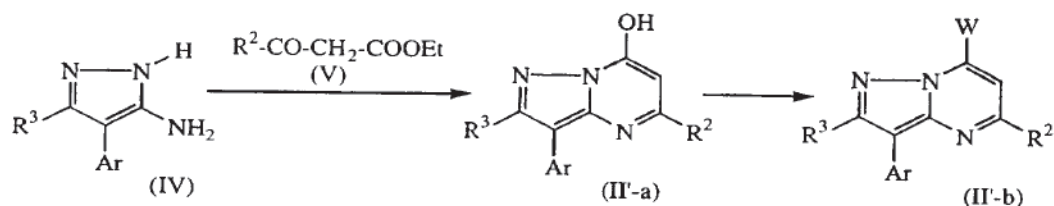


15 wherein in the above reaction schemes the radicals R¹, R², R³, R⁵ and Ar are as defined in claim 1 and W is an appropriate leaving group;

or, if desired, converting compounds of formula (I) into each other following art-known transformation reactions; and further, if desired, converting the compounds of formula (I), into an acid addition salt by treatment with an acid, or conversely, converting the acid addition salt form into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

13. A process of preparing a compound of formula (II') as claimed in claim 10
characterized by
 25 reacting an intermediate of formula (IV) with a β -keto ester (V) in a reaction-inert
 solvent, thereby yielding compounds of formula (II'-a), defined as compounds of
 formula (II') wherein W' is hydroxy;

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and optionally converting compounds of formula (II'-a) into compounds of formula (II'-b), defined as compounds of formula (II') wherein W' is other than hydroxy;

5 wherein in the above reaction schemes the radicals R^2 , R^3 and Ar are as defined in claim 1 and W' is hydroxy, halo, mesyloxy or tosyloxy;

or, if desired, converting compounds of formula (II') into each other following art-known transformation reactions; and further, if desired, converting the compounds
 10 of formula (II'), into an acid addition salt by treatment with an acid, or conversely, converting the acid addition salt form into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/EP 97/00459

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 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 6 C07D

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.
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X	JP 42 011 753 A (SHIONOGI AND CO., LTD.) 1967 cited in the application see the whole document & CHEMICAL ABSTRACTS, vol. 67, no. 23, 4 December 1967 Columbus, Ohio, US; abstract no. 108663r, see abstract	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search 15 May 1997	Date of mailing of the international search report 29. 05. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer De Jong, B

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page 1 of 2

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/EP 97/00459

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. MED. CHEM. (1976), 19(4), 512-16 CODEN: JMCMAR, 1976, XP002030876 NOVINSON, THOMAS ET AL: "Novel heterocyclic nitrofurfural hydrazones. In vivo antitrypanosomal activity" see page 516, compounds 7a, 7b ---	11
X	J. MED. CHEM. (1981), 24(5), 610-13 CODEN: JMCMAR; ISSN: 0022-2623, 1981, XP002030877 SENGA, KEITARO ET AL: "Synthesis and antischistosomal activity of certain pyrazolo[1,5-a]pyrimidines" see Table II, no. 33,35 ---	11
A	WO 94 13677 A (PFIZER ;CHEN YUHPYNG LIANG (US)) 23 June 1994 cited in the application see claims -----	1-13

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page 2 of 2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No

PCT/EP 97/00459

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 9413677 A	23-06-94	AU 5728194 A	04-07-94
		CA 2150709 A	23-06-94
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		ZA 9309405 A	15-06-95



Imidazopyridazine compounds

Abstract

translated from Japanese

The present invention relates to novel compounds of formula I substituted imidazo [1,2-b] pyridazine compounds, pharmaceutical compositions thereof, corticotropin releasing factor 1 (CRF1) receptor antagonists, etc., for mental disorders and neurological diseases. Relates to use in therapy.

Formula I

Classifications

⌘ C07D487/04 Ortho-condensed systems

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Japan

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Other languages: Japanese

Inventor: ヘザー・ジャネル・バーボサ, エリザベス・アーロン・コリンズ, チャフィク・アムドゥチ, エリック・ジェイムズ・ヘンバー, フィリップ・アーサー・ヒップスカインド, リチャード・デュエイン・ジョンストン, ル・ジャンリアン, マイケル・ジョン・ラップ, 養子高&薬, リチャード・クレイグ・トンプソン

Worldwide applications

2006 WO US MX CA KR PT JP PL BR CN EP EA AG DK ES DE SI AT 2007 IL ZA TN GR NG MA 2009 CY

Application JP2008503062A events ⓘ

Priority claimed from US6538160BP

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2012-07-11 Application granted

2012-07-11 Publication of JP4971300B2

Status Expired - Fee Related

2026-03-20 Anticipated expiration

Info: Patent citations (7), Cited by (50), Legal events, Similar documents, Priority and Related Applications

External links: Espacenet, Global Dossier, Discuss

Claims (10)

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translated from Japanese

Compounds of formula I and their pharmaceutically acceptable salts:

Formula I

Wherein R⁰ is hydrogen, halo, methyl or ethyl, R¹ and R² are independently methyl, methoxy, or trifluoromethyl, and R² is

R⁴ is hydrogen, halo, or hydroxy, R^{5a} and R^{5b} are independently ethyl or n-propyl, and R⁶ is independently hydrogen, halo in each case, Cyano, (C₁-C₄) alkyl, trifluoromethyl,

methoxy, or phenyl and R⁷ is hydrogen, halo, methyl, methoxy, dimethylamino,

And R⁸ is hydrogen, halo, cyano, (C₁-C₄) alkyl, R⁹ R¹⁰ N-, carbamyl, (C₁-C₂) alkoxy (C₁-C₂) alkyl, R¹¹ -C(O)-,

R¹¹ is methoxy, methylamino, dimethylamino, or phenyl, and R¹² is hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy dimethylamino, acetyl, Or

methylsulfonyl, R¹³ is hydrogen, methyl or halo, R¹⁴ is hydrogen or hydroxy, R¹⁵ is methylthio, cyclopropyl, phenyl,

R⁹ is (C₁-C₅) alkyl, (C₃-C₅) cycloalkyl, methoxy (C₂-C₄) alkyl substituted with hydrogen, cyano, formyl, vinyl, or ethynyl, acetyl, (C₁-C₂) alkylsulfonyl, (C₃) alkoxyl, R¹⁵ -CH₂ n-, or (C₁-C₂) alkyl Rb is hydrogen or (C₁-C₃) Alkyl, X is -CH₂-, -CO-, -O-, -S- or -SO₂-, Y is -CH₂- or -O-, and Z is S or O, n is 1 or 2, Q is hydrogen or methyl, T is hydrogen

or methyl, J is methyl, trifluoroethyl, or tert-butyl, and M is, Methyl or halo). The compound according to claim 1, wherein R⁰ and R⁴ are hydrogen, R¹ and R² are methyl, and R^{5a} and R^{5b} are ethyl, R² is

The compound according to claim 1 or 2, wherein z is S, selected from the group consisting of. The compound according to any one of claims 1 to 3, wherein R⁷ is hydrogen. The

compound according to any one of claims 1 to 4, wherein R⁶ is halo or methyl. R⁸ is

And X is O. The compound according to any one of claims 1 to 5. A pharmaceutical composition comprising the compound according to any one of claims 1 to 6 or a

pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. The compound according to any one of claims 1 to 6, which is used for a

pharmaceutical product. Use of a compound according to any of claims 1 to 6 for the manufacture of a medicament for the treatment of anxiety, depression, major depression

disorder, alcohol withdrawal symptoms or irritable bowel syndrome in mammals. The use according to claim 9, wherein said mammal is a human.

Description

translated from Japanese

The present invention relates to novel substituted imidazo [1,2-b] pyridazine compounds, pharmaceutical compositions thereof, and the use of such compounds as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric and neurological disorders about.

Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is a major physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland (J. Rivier et al., Proc. Natl. Acad. Sci (USA) 80: 4851 (1983); W. Vale et al., Science 213: 1394 (1981)). In addition to the role of the endocrine system in the pituitary gland, the hormones are widely distributed outside the hypothalamus in the central nervous system, consistent with the role of neurotransmitters or neuromodulators in the brain. It has been shown by immunohistochemical localization of CRF (W. Vale et al., Rec. Prog. Horm. Res. 39: 245 (1983); GF. Kooib, Persp. Behav. Med. 2: 39 (1985); EB De Souza et al., J. Neurosci. 5: 3189 (1985)). There is also evidence that CRF plays an important role in perfecting the immune system's response to physiological, psychological, and immunologically invasive factors (JE Blackcock, Physiological Reviews 69: 1 (1989); JE Morley, Life Sci. 41: 527 (1987)).

There is evidence that CRF plays a role in psychiatric and neurological disorders including depression, anxiety related disorders and eating disorders. The pathogenesis and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis are also related to dysfunction of CRF neurons in the central nervous system. A role has been presumed (for review see EB De Souza, Hosp. Practice 23:59 (1986)). Furthermore, CRF is widely distributed outside the hypothalamus within the CNS, and is known to contribute to a wide range of autonomous behavioral effects and physiological effects (see, for example, Vale et al. 1983; Kobb, 1985, and EB De Souza et al., 1985). For example, CRF concentrations are significantly increased in cerebrospinal fluid of patients with affective disorders or major depression (CB Nemerov et al., Science 226: 1342 (1984); CM Banki et al., Am. J. Psychiatry 144: 873 (1987); RD France et al., Biol. Psychiatry 28:85 (1988); M. Arato et al., Biol. Psychiatry 25: 355 (1989). Furthermore, excessive levels of CRF are known to produce anxiolytic effects in animal models (see, e.g. Britton et al., 1982; Berridge and Dunn, 1986 and 1987).

In the suicide frontal cortex, the density of CRF receptors is significantly reduced consistent with CRF hypersecretion (CB Nemerov et al., Arch. Gen. Psychiatry 45: 577 (1988)). Furthermore, a slowing of the adrenocorticotrophic hormone (ACTH) response to CRF (intravenous administration) is observed in depressed patients (PW Gold et al., Am. J. Psychiatry 141: 619 (1984); F. Holtsboer et al., Psychoneuroendocrinology 9: 147 (1984); PW Gold et al., New Engl. J. Med. 314: 1129 (1986)). Preclinical studies in rats and non-human primates further support the hypothesis that hypersecretion of CRF may be involved in symptoms observed in human depression (RM Sapolsky, Arch. Gen. Psychiatry 46: 1047 (1989)). There is also evidence that tricyclic antidepressants can alter CRF levels, thereby changing the number of receptors in the brain (Grigoriadis et al., Neurosychopharmacology 2:53 (1989)).

Neurochemical, endocrine system, and receptor binding studies all demonstrate the interaction of CRF with benzodiazepine anxiolytics and provide further evidence for the involvement of CRF in these disorders. Chlordiazepoxide is a conflict test in rats [K. T.A. Britton et al., Psychopharmacology 86: 170 (1985); T.A. Britton et al., Psychopharmacology 94: 306 (1988)] and the auditory startle test [N. R. Swedlow et al., Psychopharmacology 88: 147 (1986)] both attenuate the "anxiety-inducing" effect of CRF. In the operant conflict study, the benzodiazepine receptor antagonist Ro15-1788 alone had no behavioral activity, but reversed the effect of CRF in a dose-dependent manner, whereas the benzodiazepine inverse agonist FG7142 enhanced the action of CRF. (K. T. Britton et al., Psychopharmacology 94: 396 (1988)). Preliminary studies using alpha-helix sheep CRF (9-41), a putative CRF receptor antagonist, in a variety of behavioral paradigms, this antagonist provides "anxiolytic-like" effects qualitatively similar to benzodiazepines (CW Berridge and AJ Dunn, Horm. Behav. 21: 393 (1987); Brain Research Reviews 15:71 (1990)).

CRF receptor subtypes CRF1 and CRF2 have been identified and these are heterogeneously distributed in the brain [D. T.A. Chalmers et al., J. TPS 17: 166-72 (1996)], suggesting potential functional diversity (SC Heinrichs et al., Regul. Peptides 71:15 (1997)). For example, the widely distributed brain CRF1 receptor is strongly involved in emotional associated exposure to environmentally invasive factors (G. Liebsch et al., Regul. Peptides 59: 229-39 (1995); W. Schulz, PNAS 93: 10477-82 (1996)). Notably, CRF1 receptor but not CRF2 appears to mediate significant anxiety-like behavior (Heinrichs et al., 1997). More discrete septum / hypothalamus distribution [D. T.A. Chalmers et al. J. et al. Neurosci. 15 (10): 6340-50 (1995)], and the availability of selectable endogenous ligands [J. Vaughan et al., Nature 378: 287-92 (1995)] suggest a completely different functional role for the CRF2 receptor (Heinrichs et al., 1997). For example, a novel CRF-family neuropeptide with a superior affinity for CRF2 over the CRF1 receptor has been reported to suppress appetite without producing the behavioral activation profile observed with selective CRF1 activation. (H. Tezval et al., PNAS 101 (25): 9468-9473 (2004)). In many cases, CRF2 activation results in effects similar to those reported for CRF1 antagonists or CRF1 gene deletions (SC Heinrichs, Trends in Pharmaceutical Sciences 20 (8): 311-5 (1999)). CRF2 agonists have been proposed as obesity inhibitors, but CRF1 antagonists may also be important in the treatment of obesity (C. Contoreggi et al., Neuroendocrinology 80 (2): 111-23 (2004)).

In view of the above, effective and selective antagonists of CRF1 are desirable as potentially valuable therapeutics for the treatment of psychiatric and neurological disorders. Thus, discovery of new CRF1 antagonists is desired.

The compounds of the present invention include CRF1 receptor antagonists. One embodiment of the invention is a compound of formula I and pharmaceutically acceptable salts thereof.

Formula I

Wherein R⁰ is hydrogen, halo, methyl, or ethyl, R¹ and R² are independently methyl, methoxy, or trifluoromethyl, and R³ is

R⁴ is hydrogen, halo, or hydroxy, R^{5a} and R^{5b} are independently ethyl, or n-propyl, and each of R⁶ is independently hydrogen, Halo, cyano, (C₁-C₄) alkyl, trifluoromethyl,

methoxy, or phenyl and R⁷ is hydrogen, halo, methyl, methoxy, dimethylamino,

R⁸ is hydrogen, halo, cyano, (C₁-C₄) alkyl, R⁹ R¹⁰ N-, carbamyl, (C₁-C₂) alkoxy (C₁-C₂) alkyl, R¹¹-C(O)-,

R¹¹ is selected from the group consisting of: R¹¹ is methoxy, methylamino, dimethylamino, or phenyl, R¹² is hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxydimethylamino, acetyl, Or methylsulfonyl, R¹³ is hydrogen, methyl, or halo, R¹⁴ is hydrogen or hydroxy, R¹⁵ is methylthio, cyclopropyl, phenyl,

R¹⁶ is (C₁-C₅) alkyl, (C₃-C₅) cycloalkyl, methoxy (C₂-C₄) alkyl substituted with hydrogen, cyano, formyl, vinyl, or ethynyl, acetyl, (C₁-C₂) alkyl sulfonyl, (C₃) alkenyl, R¹⁷ is (CH₂)₂ n-, or (C₁-C₂) alkyl, R¹⁸ is hydrogen or (C₁-C₂) alkyl, X is -CH₂-, -CO-, -O-, -S-, or -SO₂-, and Y is -CH₂-, or -O-, Z is S or O, n is 1 or 2, Q is hydrogen or methyl, T is hydrogen or methyl, J is methyl, trifluoroethyl, Or tert-butyl, and M is methyl or halo

Another embodiment of the invention is a compound of formula I, wherein R⁰ and R⁴ are hydrogen, R¹ and R² are methyl, and R^{5a} and R^{5b} are ethyl.

Yet another embodiment of the present invention is a compound of formula I, wherein R² is Selected from the group consisting of (Wherein Z is S)

A further embodiment of the invention is a compound of formula I, wherein R⁷ is hydrogen.

Another embodiment of this invention is a compound of formula I, wherein R⁸ is halo, or methyl.

Yet another embodiment of the present invention is a compound of formula I, wherein R⁹ is R is, (Wherein X is O)

Another embodiment of the invention is a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent or excipient.

Yet another embodiment of the present invention is a compound of formula I for use as a medicament.

A further embodiment of the present invention is the use of a compound of formula I for the manufacture of a medicament for the treatment of anxiety, depression, major depressive disorder, alcohol withdrawal, or irritable bowel syndrome in a mammal, is there, in yet another embodiment, the mammal is a human.

Throughout the foregoing and description of the invention, the following terms will be understood to have the following meanings unless otherwise indicated. "Alkoxy" means an alkyl-O- group in which the alkyl group is as described herein. Specific alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, and n-butoxy. "Alkyl" means a saturated aliphatic hydrocarbon group which may be straight or branched having 1 to 5 carbon atoms in the chain. "Alkenyl" means an unsaturated aliphatic hydrocarbon group which may be straight or branched having 2 to 4 carbon atoms in the chain. "Cycloalkyl" is a monocyclic group having from 3 to 5 carbon atoms. "Halo" means fluoro, chloro, bromo, or iodo. "Pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid and base addition salts of the compounds of this invention. These salts can be prepared in situ during the final isolation and purification of the compounds. In particular, it can be prepared by reacting the purified compound in free base form with a suitable organic or inorganic acid and isolating the salt formed. Specific acid addition salts include hydrobromide, hydrochloride, sulfate, disulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearin Acid salt, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleic acid, fumarate, succinic acid, tartrate, naphthylate, mesylate, glucoheptanoate, Lactinobionate, sulfamate s, malonate s, salicylate, propionate s, methylene-bis-b hydroxynaphthoate, gentisate, isethionate s, di-p-toluate tartrate, tartaric acid Toluoyl, methanesulfonate, ethanesulfonate, benzenesulfonate s, p-toluenesulfonate s, cyclohexyl sulfamate, and Laurylsulfate Kins salts. S. M.M. Berge, et al. "Pharmaceutical Salts," Pharm. Sci. 66, 1-19 (1977). A list of suitable salts can be found in Remington's Pharmaceutical Sciences, 17th ed. Mack Publishing. Company, Easton, Pa. 1928, p. 1418 can be found.

As used herein, it will be understood that reference to a compound of formula I is intended to encompass pharmaceutically acceptable salts thereof. A "therapeutically effective amount" or "effective amount" is an amount of a compound of formula I of the invention, or a pharmaceutical composition containing a compound of formula I of the invention, which may be a researcher, veterinarian, doctor, or other Means a biological or pharmaceutical response to a tissue, system, animal, or human being studied by a clinical physician, or an amount that will exhibit the desired therapeutic effect.

The terms "treatment", "treat", "treating" and the like are meant to encompass both delaying or ameliorating disease progression. These terms also include the alleviation, amelioration, alleviation, elimination or reduction of one or more symptoms of a disease or symptom, even though the disease or symptom is not substantially eliminated and the progression of the disease or symptom itself is not delayed or recovered. To do, "Treatment" and like terms also include prophylactic (eg. prophylactic) and palliative treatment. Prevention of a disease is performed by delaying or delaying the onset of the disease.

The symbol "-" in the molecular structure refers to the position to which a particular substituent is attached.

When a variable occurs more than once in any structure or Formula I, the definition in each case is independent of the definition in the other cases. Also, combinations of substituents and / or variables are permissible only if the combination results in a suitable compound. When selecting a compound of the invention, one skilled in the art will understand that the various substituents, ie R¹, R², etc., should be selected to be consistent with the well-known rules of chemical structure bonding. Let's go.

Under standard nomenclature used throughout this specification, we begin by naming the terminal portion of the designated side chain and then by the adjacent functional group to the attachment moiety. For example, an arylcarbonylaminoalkyl substituent corresponds to aryl-C(=O)-NH-alkyl.

The present invention contemplates a particular class of compounds of formula I. The following paragraphs describe such specific classes.

(A) R⁰ is hydrogen;

(B) R¹ is methyl;

(C) R³ is methyl;

(D) R¹ and R³ are methyl;

(E) R² is

And

(F) R² is

And

(G) R⁴ is hydrogen;

(H) R^{5a} is ethyl;

(I) R^{5b} is ethyl;

(J) R^{5a} and R^{5b} are ethyl;

(K) R⁶ is halo;

(L) R⁶ is methyl;

(M) R⁷ is hydrogen;

(N) R⁸ is

And

(O) R⁸ is

R is.

When all compounds of formula I are useful CRF1 receptor antagonists, the following paragraphs describe a more specific class.

(A) each of R¹ and R³ is methyl, each of R^{5a} and R^{5b} is ethyl,

(B) R¹ and R³ are methyl, R^{5a} and R^{5b} are ethyl, R⁰ is hydrogen,

(C) R¹ and R³ are methyl, R^{5a} and R^{5b} are ethyl, R⁰ and R⁴ are hydrogen,

(D) R² is

And R⁷ is hydrogen,

(E) R² is

R⁷ is hydrogen, R⁶ is halo,

(F) R² is

R⁷ is hydrogen, R⁶ is methyl,

(G) R² is

R⁷ is hydrogen, R⁶ is halo or methyl, R⁸ is

And

(H) R² is

And R⁶ is halo,

(I) R² is

R⁶ is methyl;

(J) R² is

R⁶ is halo or methyl and R⁸ is

(K) R² is

R⁶ is halo or methyl and R⁸ is

It is.

The following paragraphs describe a more specific class of CRF1 receptor antagonists of the present invention.

(A) R¹ and R³ are methyl, R^{5a} and R^{5b} are ethyl, R⁰ and R⁴ are hydrogen, and R² is

R⁷ is hydrogen, R⁶ is halo or methyl, R⁸ is

And

(B) R¹ and R³ are methyl, R^{5a} and R^{5b} are ethyl, R⁰ and R⁴ are hydrogen, and R² is

R⁷ is hydrogen, R⁶ is halo, R⁸ is

And

(C) R¹ and R³ are methyl, R^{5a} and R^{5b} are ethyl, R⁰ and R⁴ are hydrogen, and R² is

R⁷ is hydrogen, R⁶ is methyl, R⁸ is

And

(D) R¹ and R³ are methyl, R^{5a} and R^{5b} are ethyl, R⁰ and R⁴ are hydrogen, and R² is

R⁶ is halo or methyl and R⁸ is

And

(E) R¹ and R³ are methyl, R^{5a} and R^{5b} are ethyl, R⁰ and R⁴ are hydrogen, and R² is

R⁶ is halo and R⁸ is

And

(F) R¹ and R³ are methyl, R^{5a} and R^{5b} are ethyl, R⁰ and R⁴ are hydrogen, and R² is

R⁶ is halo and R⁸ is

And

(G) R¹ and R³ are methyl, R^{5a} and R^{5b} are ethyl, R⁰ and R⁴ are hydrogen, and R² is

R⁶ is methyl and R⁸ is

And

(H) R¹ and R³ are methyl, R^{5a} and R^{5b} are ethyl, R⁰ and R⁴ are hydrogen, and R² is

R⁶ is methyl and R⁸ is

It is.

Preferably, the compounds of the present invention exhibit a CRF1 binding Ki value of 1 micromolar or less, more preferably 500 nanomolar or less. Even more preferably, the compounds of the present invention exhibit CRF1 binding Ki values of 250 nanomolar or less, more preferably 100 nanomolar or less. More preferably, the compounds of the present invention exhibit a CRF1 binding Ki value of 30 nanomolar or less, more preferably 15 nanomolar or less. Most preferably, the compounds of the present invention exhibit a CRF1 binding Ki value of 5 nanomolar or less.

The present invention also provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent or excipient. A "pharmaceutically acceptable carrier, diluent or excipient" is a generally acceptable vehicle for delivering a bioactive substance to a mammal (eg, a human). Such carriers are generally formulated according to a number of factors that should be determined and considered within the ordinary knowledge. These factors include, but are not limited to, the type and nature of the active substance being formulated, the subject to whom the composition containing the active substance is to be administered, the intended route of administration of the composition, and the target. The therapeutic index is given. Pharmaceutically acceptable carriers and excipients include aqueous and non-aqueous liquid media, and various solid and semi-solid dosage forms. Such carriers can contain, in addition to the active substance, a number of different ingredients and additives, such additional ingredients being formulated during formulation for various reasons well known to those skilled in the art (eg, stabilization of the active substance). Descriptions of suitable pharmaceutically acceptable carriers to be added, and factors related to their selection, can be found in readily available literature (eg Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa), 1985).

These compounds of formula I are unit doses of formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles, orally, topically, parenterally, or rectally by inhalation or spray. May be administered.

A pharmaceutical composition containing a compound of general formula I is in a form suitable for oral use, for example tablets, troches, drops, liquid or oily suspensions, dispersed powders or granules, emulsions, hard capsules or soft It may be in the form of a capsule or syrup or elixir.

Suitable dosage forms for administration generally contain from about 1 mg to about 300 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will usually be present in an amount of about 0.5-95% based on the total weight of the composition. Appropriate coatings may be used to improve palatability or delay absorption.

The compounds of formula I are antagonists of the CRF1 receptor and are useful in the treatment of anxiety disorders, depression, major depressive disorder, and stress related disorders. Anxiety disorders are a group of diseases recognized in the art, including phobias, anxiety conditions, post-traumatic stress disorders, and atypical anxiety disorders [The Merck Manual of Diagnosis and Therapy, 16th edition (1992)]. Emotional stress is usually an exacerbating factor in anxiety disorders, which typically respond to drugs that reduce the response to stress. This compound is also useful in smoking cessation plans. The method of treatment involves administering to a mammal (eg, a human) an effective amount of a compound of formula I. In particular, a therapeutically effective amount of a compound of this invention is effective

in antagonizing or reducing corticotropin releasing factor (CRF) levels in a mammal (eg, a human), and thereby characterized by an abnormal CRF expression level. The amount to relieve symptoms.

Thus, the present invention is a method of treating a symptom that is treatable by reducing CRF1 receptor stimulation, wherein a mammal (eg, human) in need thereof is treated with a compound of formula I or a pharmaceutically acceptable salt thereof. A method comprising administering an effective amount to antagonize CRF1 receptor stimulation.

The invention also provides the use of a compound of formula I for the manufacture of a medicament for the treatment of a condition treatable by reducing CRF1 receptor stimulation.

The present invention also provides a method of antagonizing CRF1 receptor in a warm-blooded animal comprising administering a compound of the present invention to the animal in an effective amount to antagonize CRF1 receptor. The warm-blooded animal is preferably a mammal, more preferably a human.

The present invention is a method of treating a disease in a warm-blooded animal, wherein the disease exhibits hypersecretion of CRF, or the treatment of the disease can be achieved or promoted by antagonizing the CRF1 receptor, the method comprising: Also provided is a method comprising administering to the animal a therapeutically effective amount of a compound of the invention. The warm-blooded animal is preferably a mammal, more preferably a human.

The compounds of formula I or pharmaceutically acceptable salts thereof are useful for the treatment of various diseases and conditions in mammals (eg humans), such as social anxiety neuropathies; panic diseases Obsessive-compulsive disorder, major anxiety disorder with comorbid depression; affective disorder; anxiety neurosis; depression; irritable bowel syndrome; post-traumatic stress disorder; supranuclear paralysis; immunosuppression; Anorexia nervosa, bulimia, or other eating disorders; drugs or alcohol withdrawal; drug abuse disorders (eg, nicotine, cocaine, ethanol, opium, or other drugs); inflammatory disorders; infertility problems; Diseases that can be achieved or promoted by (including but not limited to, diseases induced or promoted by CRF; inflammatory diseases (such as rheumatoid arthritis and osteoarthritis), pain, asthma, psoriasis Systemic anxiety disorder; panic; phobia; obsessive compulsive disorder; stress-induced sleep disorder; stress-related illness; pain perception such as fibromyalgia; major depression, major depression Mood disorders such as depression, such as sexual disorders, single episode depression, recurrent depression, child abuse-induced depression, and postpartum depression; mood modulation; manic-depressive illness; circulatory temperament; fatigue syndrome; chronic fatigue Syndrome; stress-induced headache; headache; cancer; human immunodeficiency virus (HIV) infection; neurodegenerative diseases (eg Alzheimer's disease, Parkinson's disease, Huntington's disease, Alzheimer-type senile dementia and cerebrovascular dementia), (eg, ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and postoperative ileus), and colons associated with psychopathological dysfunction or stress Agility; dietary disorders (eg anorexia nervosa and bulimia nervosa), hemorrhagic stress; stress-induced psychotic onset; normal thyroid function syndrome; inappropriate diarrhea-stopping hormone (ADH) syndrome; obesity; And metabolic syndrome; infertility; preterm birth; head trauma; spinal cord trauma; ischemic neuronal damage (eg, cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; Cardiovascular and heart related diseases such as hypertension, tachycardia and congestive heart failure; seizures; stress-induced immune dysfunction (eg stress stress-induced fever, stress-induced infection in humans and animals, swine stress syndrome, Bovine livestock pastureiosis, equine paroxysmal fibrillation, and chick dysfunction, pure sheep stress, or human animal interaction-related stress in dogs), etc. Immune dysfunction; muscle cramps, urinary incontinence, Alzheimer-type senile dementia; cerebrovascular dementia, ALS; Alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia.

The compounds of this invention are suitable agents for treating the above diseases or abnormalities by means of bringing the active substance into contact with the reaction site (eg, oral or parenteral administration) of a mammal (eg, human) in vivo. Can be administered using a mold. The compound can be administered by conventional available means for use with a pharmacological ether either as a therapeutic agent alone or in combination with a therapeutic agent. The compounds can be administered alone, but will generally be administered with a pharmacological carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

Therapeutically effective amounts of the compounds of the present invention for the treatment of the above diseases or disorders in warm-blooded animals can be determined by various methods known to those skilled in the art, for example, various amounts of a specific drug in an animal suffering from a specific condition. To determine the effect on this animal. Typically, a therapeutically effective amount of a compound of this invention can be administered orally daily at a dose of 0.002-200 mg / kg body weight of active ingredient. Usually, divided doses of 1 to 4 doses / day, 0.01 to 10 mg / kg, or sustained release formulations are effective to obtain the desired pharmacological effect. However, the specific dose level of a particular patient depends on the activity, age, weight, overall health, sex, diet, time of administration, route of administration, and excretion of the specific compound used, drug combination, and it will be understood that it will vary depending on various factors such as severity. The frequency of administration may also vary depending on the compound used and the particular disease to be treated. However, in the treatment of most CNS diseases, a dosage regimen of 4 times daily or less is preferred. In the treatment of stress or depression, a dosage regimen of once or twice daily is particularly preferred.

It will be understood that all combinations of the specific and preferred embodiments described above and the following examples are intended to be included in the present invention unless they include inconsistent groups. Furthermore, all examples described herein are for illustrative purposes and are not intended to limit the invention in any way.

The compounds of the invention can generally be prepared using the routes of administration described in the following schemes. Starting materials can be prepared by these schemes or procedures well known to those skilled in organic chemistry. The variables used in the scheme are as follows or as claimed.

One skilled in the art will appreciate that the introduction of certain substituents creates asymmetry in the compounds of Formula I. The present invention encompasses all enantiomers and mixtures of enantiomers and stereoisomers and is in a sterically pure form (eg, geometrically pure, enantiomerically pure, or diastereomeric. Pure) and enantiomeric and stereoisomeric mixtures such as racemates. Enantiomeric and stereoisomeric mixtures can be obtained by well-known methods (such as chiral phase gas chromatography, chiral phase high performance liquid chromatography, or crystallization of compounds as chiral salt complexes), and their enantiomers or stereoisomers. It can be separated into the body. Enantiomers and stereoisomers can also be obtained from enantiomerically pure intermediates, reagents and catalysts by well-known synthetic methods.

Pharmaceutically acceptable salts are intended to be within the scope of the present invention. The compound of the present invention is a salt of a compound that can be formed with a base and an acid, for example, an inorganic acid salt such as hydrochloric acid, or an organic acid salt such as trifluoroacetic acid. The compounds of this invention can be prepared by using reactions as shown in the following schemes, in addition to standard procedures known in the literature or embodied by experimental procedures. Accordingly, these schemes are not limited by the compounds listed for illustrative purposes and the particular substituents used.

Scheme 1

Synthesis of imidazo [1,2-b] pyridazine fragments

R¹, R³, R^{5a}, and R^{5b} are as described above.

In Scheme 1, substituted 3-amino-pyridazines 1 are acylated from room temperature to reflux using a pivaloyl halide and a base such as triethylamine in a polar aprotic solvent such as methylene chloride. To obtain amide 2. Treatment of amide 2 with Grignard reagent in diethyl ether or THF provides 4-substituted amide 3. Amide 3 is

hydrolyzed with aqueous HCl at room temperature to 110 ° C. and then neutralized to give free amine 4. Amine 4 is treated with an alpha-haloketone and a base such as sodium bicarbonate in 95% ethanol at room temperature to 110 ° C. to give imidazopyridazine 5. Imidazopyridazine 5 is treated with a halogenating reagent such as N-iodo or N-bromosuccinimide at 0 ° C. to room temperature in a polar aprotic solvent (eg acetonitrile) to give halide 6. Halide 6 undergoes halogen metal exchange at -78 ° C. to room temperature with an alkyl lithium reagent such as n-, sec-, or tert-butyllithium in diethyl ether or THF, followed by, for example, trimethyl borate. Treatment with trialkyl borate provides the intermediate boronic ester, which is hydrolyzed with aqueous HCl to give boronic acid 7.

Scheme II

Synthesis of a compound of formula I with a transition metal catalyst Scheme I

Reaction formula 2

in the formula, R²-U is

Selected from the group consisting of

Reaction formula 3

Reaction formula 4

in the formula, R²-H is

Selected from the group consisting of

Reaction formula 5

Reaction formula 6

Reaction formula 7

in the formula, R²-H^b is

Selected from the group consisting of R¹, R², R³, R^{5a}, R^{5b}, R⁶, R⁷, R⁸, U, and z are as described above.

In Scheme II, Formula 1, halide 6 is a 5-membered compound in a lower alkanol (methanol or n- or i-propanol) / DME mixture in the presence of a palladium catalyst such as tetrakis-triphenylphosphine palladium (0). The compound of formula I can be obtained in a coupling reaction with ring heterocyclic boronic acid 8 at 70-120 ° C.

Alternatively, in Formula 2, boronic acid 7 is converted into a lower alkanol (methanol or n- or i-propanol) / DME mixture in a 5-membered heterocyclic halide 9 and, for example, tetrakis-triphenylphosphine palladium (0), etc. The compound of formula I can be obtained in a coupling reaction using a palladium catalyst of 70 to 120 ° C.

In Formula 3, a 5-membered heterocyclic halide 9 is subjected to halogen-lithium exchange with, for example, n-, sec- or tert-butyllithium in THF or ether at -65 ° C, and then diethyl ether or THF. Among these, lithium zinc exchange with ZnCl₂ may be performed at a temperature up to room temperature. The in situ organozinc reagent 10 is then coupled with halide 6 at 70-120 ° C. in the presence of palladium, such as PdCl₂(dppf), in THF to give a compound of formula I. May be.

In Formula 4, the 5-membered heterocycle with a ring proton is in THF or ether, for example, from -65 ° C. to room temperature with either alkyl lithium such as n-, sec- or tert-butyl lithium, or lithium diisopropylamide. May be lithiated with, followed by lithium-zinc exchange with anhydrous zinc halide in diethyl ether or THF to obtain the organozinc reagent 10 used as in Formula 3 above. One skilled in the art should also appreciate that commercially available organozinc reagents 10 can be used directly as organozinc coupling partners.

Further with respect to Formula 5, it may be advantageous or convenient to directly convert the 5-membered heterocyclic halide 9 to the organozinc reagent 10 using Reike Zn in THF for coupling with halide 6.

In Formula 6, the 5-membered heterocyclic halide 9 is a DME, THF, NMP solvent such as Pd₂(dba)₃, PdCl₂, palladium acetate / TDBPP, or tetrakis-triphenylphosphine palladium (0). Coupling with imidazo[1,2-b]pyridazine intermediate 5 directly in the presence of palladium at 70-120 ° C. can give compounds of formula I.

Alternatively, with respect to Formula 7, in DME, THF, or NMP solvent, imidazo[1,2-b]pyridazine halide 6 may be coupled to 5-membered heterocycle 11 to give a compound of formula I.

Scheme III

Synthesis of substituted 5-membered heterocyclic halides

R⁶, R⁷, R⁸, t, and z are as described above

Some 5-membered heterocyclic rings and / or their bromides and / or iodides useful as starting materials for the synthesis of compounds of formula I are commercially available or prepared by methods well known by those skilled in the art. May be. With respect to Scheme III, they may be prepared by halogenation, for example using bromine, NBS or NIS. In addition, some of intermediates 11 and 12 may be prepared by lithium halogen exchange followed by quenching with water.

Compounds of formula I as intermediates in the preparation of other compounds of formula I include aryllithium reagents to carbonyl compounds such as aldehydes, ketones, esters, and wine levamides (by the methods of formulas 3 and 4 of Scheme II). Generation) addition. The resulting carbinol or carbonyl compound is further modified by halogenation under acidic conditions and by secondary aryl lithium addition, respectively.

Abbreviated TBDMSCl, or TBDMSiCl-tert-butyl - dimethylsilyl chloride MS (ES) - Electrospray Mass spectrum THF- tetrahydrofuran DMSO- dimethylsulphoxide DMF- dimethylformamide DCM, CH₂Cl₂ - dichloromethane dioxane-1,4-dioxane N₂- Nitrogen gas NIS-N-iodosuccinimide NBS-N-bromosuccinimide MeOH-methanol EtOH-95% ethanol RBF, RB-round bottom flask RBN-round bottom one-neck flask SiO₂-silica gel EtOAc, AcOEt-ethyl acetate GFF-glass microfiber filter HPLC-high pressure liquid chromatography on silica gel ISCO-low pressure liquid chromatography on silica gel AcCl-salt Acetyl LDA-diisopropylamine lithium KOAc-potassium acetate TBAB-tetrabutylammonium bromide NMP-N-methylpyrrolidinone TDBPP-tris (2,4-di-1-butylphenyl) phosphite Pd₂(dba)₃-tris (dibenzylideneacetone) } Dipalladium PdCl₂(dppf) - dichloro (diphenylphosphinoferrocene) palladium tetrakis-tetrakis- (triphenylphosphine) -palladium Dppf-1,1'-bis (diphenylphosphino) ferrocene
r. t. RT-room temperature

Unless otherwise stated, one skilled in the art will be able to best practice the invention using the above description. Examples are provided below to illustrate the present invention in further detail. These examples are intended to illustrate the present invention and are not intended to be limiting in any way. Examples 1-255 provide specific compounds and illustrate their preparation. Examples AD illustrate various biological assays that can be used to determine the biological properties of the compounds of the invention. Those skilled in the art will appropriately recognize appropriate variations from the procedures described in the embodiments.

Example 1

Preparation of 8- (1-ethyl propyl) -3- (2,4-dimethyl-5 thiazolyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine

A. 6-Methyl-pyridin-3-ylamine 3-Chloro-6-methylpyridazine (25.0 g, 0.229 moles) is dissolved in 250 mL NH₄OH and heated to 170 ° C. in a sealed container over 24 hours. Evaporate the solvent. The residue is triturated in dichloromethane and the solid is filtered. This grinding procedure is repeated four times with the filtrate.

Combine the filtered solids and dry overnight in a vacuum oven to afford the title compound as an off-white solid, 4.32 g (0.040 moles, 20%). ¹H-NMR (dmsO-d₆): δ 7.1 (d,

J = 8.9 Hz, 1H); 6.67 (d, J = 8.9 Hz, 1H); 6.04 (s, br, 2H); 2.33 (s, 3H) ppm. ES + = 110 (100%, M + 1).

8. 2,2-Dimethyl-N-(6-methyl-pyridazin-3-yl)-propionamide Method 1

7.12 g (0.065 mol) of 6-methyl-pyridin-3-ylamine in 170 ml of dry dichloromethane is added to the dry flask. 14.5 ml of triethylamine is then added and the reaction is cooled to 0 °C. Pivaloyl chloride (2.7 ml, 1.2 eq) is carefully added and the reaction is stirred for 10 minutes, removed from the solution and stirred for an additional 4 hours. Dichloromethane (200 mL) is added and the reaction is washed 3 times with saturated aqueous sodium bicarbonate and then with brine. The organic layer is dried over sodium sulfate, filtered and evaporated to an oil. The crude product is purified via silica gel chromatography using an ethyl hexane acetate gradient to give the title compound as a white solid weighing 1.51 g (7.8 mmol, 42.7%). ¹H-NMR (DMSO-d₆) δ 10.39 (s, 1H); 8.11 (d (J = 9.30 Hz, 1H)); 7.51 (d (J = 9.29 Hz, 1H)); 2.54 (s,

3H); 1.23 (s, 9H) ppm. ES + = 194 (M + 1)

Method 2

200 mg (1.56 mmol) 3-chloro-5-methylpyridazine, 190 mg (1.87 mmol) trimethylacetamide, 14.6 mg (0.023 mmol) rac-2,2'-bis (diphenylphosphine) -1, 1'-binaphthyl, tris (dibenzylideneacetone) -dipalladium (0), 762.4 mg (2.34 mmol) of cesium carboxylate and 1.5 ml of dry tetrahydrofuran are added to the dry pressure tube. The pressure tube is purged with nitrogen and sealed. The reaction is heated at 100 °C overnight. The reaction is then cooled, diluted with dichloromethane and filtered through celite. The solvent is evaporated and the crude product is purified via silica gel chromatography using an ethyl acetate hexane gradient to give 91 mg (0.47 mmol, 30%) as a white solid.

C. N-[4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-yl]-2,2-dimethyl-propionamide Active magnesium powder (19.2 g, 0.792 mol) was added to the condenser and drops. Add to a dry 3L flask fitted with a tube. The entire apparatus is cooled by heating with a drying gun under vacuum. Add as much ether as necessary to cover the magnesium. 3-Bromopentane (100 g, 0.662 mmol) is added to a 175 ml diethyl ether addition funnel. One third of the bromopentane solution is added to the magnesium and the reaction is stirred under nitrogen until boiling occurs. The remainder is then added dropwise at a rate that the boiling phenomenon continues gently. After completion of the boiling phenomenon, the reaction is stirred for 30 minutes. Then 2,2-dimethyl-N-(6-methyl-pyridazin-3-yl)-propionamide (21.3 g, 0.110 mmol) dissolved in 225 ml dry THF is added dropwise. The reaction mixture is stirred overnight. Saturated sodium tartrate (1 L) is carefully added and the reaction is stirred for 30 minutes. Transfer the reaction to a larger flask, add 2 L of ethyl acetate and stir the reaction for 1 hour. The layers are separated and the aqueous layer is extracted several times with ethyl acetate. Combine the organic extracts and evaporate the solvent. The residue is dissolved in 600 mL of dichloromethane and iodine (28 g, 0.110 mol) is added. The reaction is stirred for 2 hours. The organic layer is washed once with an aqueous solution of sodium sulfite and then with water. The organic layer is dried over sodium sulfate, filtered and evaporated to oleic acid. The crude product is purified via silica gel chromatography using a hexane ethyl acetate gradient. The component fractions are mixed and evaporated. Triturate the residue with ethyl acetate and filter the pale tan solid to give 12.0 g (45.6 mmol, 41%) of the title compound. ¹H-NMR (DMSO-d₆)

δ 9.88 (s, 1H); 7.59 (s, 1H); 2.60 (s, 3H); 2.39-2.42 (m, 1H); 1.21-1.37 (m, 2H); 1.58-1.43 (m (2H)); 1.23 (s (9H)); 0.71 (t (J = 7.49 Hz, 6H)) ppm. MS / ES + = 264

D. 4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-ylamine. N-[4-(1-ethyl-propyl)-6-methyl-pyridazin-3-yl]-2,2-dimethyl-propionamide (12.0 g, 45 mmol) is dissolved in 60 mL concentrated hydrochloric acid. The reaction is heated at 95 °C for 2 hours in a sealed flask. The reaction was poured onto ice and completed by extracting three times with ethyl acetate. Discard the organic layer and adjust the pH of the aqueous layer with 2N sodium hydroxide. The basic solution is extracted 5 times with ethyl acetate. Combine the organic extracts, dry over magnesium sulfate, filter and evaporate to give 6.68 g (37 mmol, 81%) of the title compound as a brownish oil. ¹H-NMR (DMSO-d₆) δ 6.95 (s, 1H); 5.89 (s, br, 2H); 2.52 to 2.56 (m, 1H); 2.34 (s, 3H); 1.44-1.58 (m, 4H); 0.72 (t (J = 7.04 Hz, 6H)) ppm. MS / ES + = 180 (100%, M + 1)

E. 8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine 4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-ylamine (850 mg, 4.74 mmol) Chloroacetone (3.415 mL, 5.22 mL) and 20 mL of ethanol are heated in a microwave at 110 °C for 35 minutes. Sodium bicarbonate (1.2 g, 14.2 mmol) is added and the reaction is heated in a 100 °C oil bath overnight. The solvent is evaporated and the residue is dissolved with ethyl acetate and washed three times with brine. The organic layer is dried over sodium sulfate, filtered and evaporated to a red oil. The crude product is purified via silica gel chromatography using a hexane ethyl acetate gradient. The title compound is an oil weighing 3.69 g (17.0 mmol, 84%). ¹H-NMR (DMSO-d₆) δ 7.34 (s, 1H); 6.84 (s, 1H); 2.85-3.10 (m, 1H); 2.43 (s, 3H); 2.32 (s, 3H); 1.76-1.80 (m, 4H); 0.712 (t (J = 7.49 Hz, 6H)) ppm. MS / ES + = 219 (100%, M + 2).

F. 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (5.1 g, 0.023 mol) and 50 mL of dry acetonitrile are added to the nitrogen purged flask and cooled to 0 °C. Add NIS (5.54 g, 0.025 moles) in 90 mL of dry acetonitrile. The solution is brought to room temperature and the reaction is stirred overnight. Evaporate the solvent. The residue is dissolved with ethyl acetate and washed twice with 50% aqueous sodium thiosulfate and brine. The organic layer is dried over sodium sulfate, filtered and evaporated to a residue again. The crude product is powdered with a small amount of acetonitrile and the solid is filtered off. Milling is repeated several times to give the title compound as a light tan solid weighing 7.29 g (0.021 mol, 91%). ¹H-NMR (DMSO-d₆) δ 6.96 (s, 1H); 3.0-3.3 (m, 1H); 2.51 (s, 3H); 2.35 (s, 3H); 1.71-1.80 (m, 4H); 0.71 (t (J = 7.48 Hz, 6H)) ppm. MS / ES + = 344 (100%, M + 1)

G. 8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-ylboronic acid 60 mL dry with oven dried nitrogen in a cleaned 3 neck 50 mL round bottom flask Of THF, 1.00 g (2.91 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine to -78 °C. Cooling. 4.12 mL (7.00 mmol) 1.7 M tert-butyllithium in hexane is added and the reaction is stirred at -78 °C for 1 h. 0.518 mL (7.30 mmol) of trimethyl borate is added, MS is performed after the reaction, and the TLC (1:1 hexane:EA) display of the product is observed in the mass spectrum. The reaction is stirred for an additional hour, quenched with 1N hydrochloric acid and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted 3 times with 100 mL of ethyl acetate. The extracts are combined, dried over MgSO₄, filtered and concentrated. The reaction residue is triturated with hexane and the solid is filtered off. MS, ES + = 262.2 (M + 1).

H. 8-(1-ethyl-propyl)-3-(2,4-dimethyl-5-thiazolyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine 0.340 g (1.30 mmol) of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-ylboronic acid, 0.100 g (0.521 mmol) of 5-bromo-2,4-dimethylthiazole, 0.351 g (0.313 mmol) of Pd (PPh₃)₄, 0.650 mL (1.30 mmol) of 2M aqueous Na₂CO₃, and 2 mL of 7:3:2 DME:H₂O:EtOH into a microwave pressure tube. Add and heat the mixture at 160 °C for 40 minutes. The reactants are inspected by MS indicating the presence of product. The reaction mixture is partitioned between 75 mL ethyl acetate and 75 mL water. The layers are separated and the aqueous solution is extracted with 3 x 50 mL of ethyl acetate, dried (MgSO₄) and concentrated in vacuo. The crude mixture is purified by chromatography using ethyl hexane acetate as the solvent system. The product containing the fraction is mixed to obtain 0.100 g of product with a yield of 58%. MS, ES + = 329.2 (M + 1); ¹H-NMR (DMSO-d₆) δ 6.974 (s, 1H); 3.085-3.052 (m, 1H); 2.655 (s, 3H); 2.438 (s, 3H); 2.290 (s, 3H); 2.147 (s, 3H); 1.849-1.727 (m, 4H); 0.776-0.738 (m, 6H) ppm.

Example 2

Preparation of 8-(1-ethyl-propyl)-3-(2-ethyl-4-methyl-5-yl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

A. 5-Bromo-2-ethyl-4-methylthiazol in oven cleaned N₂ in a clarified 50 mL round bottom flask, 1.00 g (7.86 mmol) of 2-ethyl-4-methylthiazol was added at room temperature. React with 0.487 mL (9.43 mmol) bromine in 7 mL acetic acid. The reaction is checked by MS after 2 hours. The reaction is partitioned between 50 mL H₂O and 25 mL CH₂Cl₂. The layers are separated and the aqueous solution is extracted with 3 x 25 mL CH₂Cl₂. Combine the organics, wash with 1 x 25 mL 1N Na₂S₂O₃, dry (MgSO₄) and concentrate in vacuo to give 1.38 g of the title compound in 85% yield. MS, ES + = 266.0 (M + 1); ¹H-NMR (DMSO-d₆) δ 2.940-2.810 (m, 2H); 2.253-2.251 (m, 3H); 1.225-1.222 (m, 3H) ppm

B. 8-(1-Ethyl-propyl)-3-(2-ethyl-4-methyl-5-thiazolyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine Using a procedure similar to Example 1H To yield 27% yield of the title product from 5-bromo-2-ethyl-4-methylthiazol. MS, ES + = 343.2 (M + 1); ¹H-NMR (DMSO-d₆) δ 6.975 (s, 1H); 3.090-3.056 (m, 1H); 3.025-2.968 (m, 2H); 2.439 (s, 3H); 2.291 (s, 3H); 2.155 (s, 3H); 1.835-1.744 (m, 4H); 1.338-1.300 (m, 3H); 0.776-0.740 (m, 6H) ppm

Example 3

Preparation of 8- (1-ethyl-propyl) -3- (2-isopropyl-4-methyl-5-thiazolyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine

A. 5-Bromo-2-isopropyl-4-methylthiazol A procedure similar to Example 2A is used to produce the title product in 90% yield from 2-isopropyl-4-methylthiazol. MS, ES + = 220.5 (M + 1); ¹H-NMR (DMSO-d₆) = 3.210-3.175 (m, 1H); 2.257 (s, 3H); 1.264-1.248 (d, 6H) ppm.

B. 8- (1-Ethyl-propyl) -3- (2-isopropyl-4-methyl-5-thiazolyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine Using a procedure similar to Example 1H To yield 29% yield of the title product from 5-bromo-2-isopropyl-4-methylthiazol. MS, ES + = 357.2 (M + 1); ¹H-NMR (DMSO-d₆) = 6.990 (s, 1H); 3.120-3.050 (m, 1H); 2.442 (s, 3H); 2.294 (s, 3H); 2.158 (s, 3H); 1.810-1.750 (m, 4H); 1.362-1.344 (d, 6H); 0.777-0.741 (m, 6H) ppm.

Example 4

Preparation of 8- (1-ethyl-propyl) -3- (4-methyl-2-phenyl-5-thiazolyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine

A. 5-Bromo-4-methyl-2-phenylthiazol A procedure similar to Example 2A is used to produce the title product in 90% yield from 4-methyl-2-phenylthiazol. MS, ES + = 256.0 (M + 1); ¹H-NMR (DMSO-d₆) = 7.900-7.867 (m, 2H); 7.538-7.512 (m, 3H); 2.407 (s, 3H) ppm.

B. 8- (1-Ethyl-propyl) -3- (4-methyl-2-phenyl-5-thiazolyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine Using a procedure similar to Example 1H To yield the title product in 24% yield from 5-bromo-4-methyl-2-phenylthiazol. MS, ES + = 391.3 (M + 1); ¹H-NMR (DMSO-d₆) = 8.005-7.995 (m, 2H); 7.538-7.534 (m, 3H); 7.010 (s, 1H); 3.185-3.095 (m, 1H); 2.490 (s, 3H); 2.394 (s, 3H); 2.316 (s, 3H); 1.895-1.785 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Example 5

Preparation of 8- (1-ethyl-propyl) -3- [4-methyl-2- (2-methyl) propyl-5-thiazolyl] -2,6-dimethyl-imidazo [1,2-b] pyridazine

A. 5-Bromo-4-methyl-2- (2-methyl) propylthiazol A 96% yield of 4-methyl-2- (2-methyl) propylthiazol was obtained using a procedure similar to Example 2A. The title product is produced. MS, ES + = 234.1 (M + 1); ¹H-NMR (DMSO-d₆) = 2.744 (m, 2H); 2.259 (s, 3H); 1.895-2.000 (m, 1H); 0.905-0.888 (m, 6H) ppm.

B. 8- (1-ethyl-propyl) -3- [4-methyl-2- (2-methyl) propyl-5-thiazolyl] -2,6-dimethyl-imidazo [1,2-b] pyridazine Example 1H and A similar procedure is used to produce the title product in 7% yield from 5-bromo-4-methyl-2- (2-methyl) propyl thiazol. MS, ES + = 371.3 (M + 1); ¹H-NMR (DMSO-d₆) = 7.013 (s, 1H); 3.109 (m, 1H); 2.892-2.875 (d, 2H); 2.517 (s, 3H); 2.513 (s, 3H); 2.476 (s, 3H); 2.197-2.073 (m, 1H); 1.868-1.780 (m, 4H); 1.018-1.002 (d, 6H); 0.813-0.775 (m, 6H) ppm.

Example 6

Preparation of 8- (1-ethyl-propyl) -3- [4-methyl-5-thiazolyl] -2,6-dimethyl-imidazo [1,2-b] pyridazine

3.00 g of 8- (1-ethyl-propyl) -3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine (8.74 mmol), 4.32 g of 4-methyl-2H Thiazol (43.6 mmol), 453 mg of triphenylphosphine (1.73 mmol) and 5.85 g of cesium carboxylate (18.0 mmol) together with 20 ml of DMF in a shield tube and N₂ gas Blow for 40 minutes. 39 mg of Pd2dba3 (0.43 mmol) is added, the tube is sealed and heated at 130 ° C. overnight. The cooled reaction mixture is filtered and applied onto a silica gel column (hexane → hexane; AcOEt = 3: 1) to give 2.12 g of the title compound (77%). ¹H-NMR (DMSO-d₆) δ 9.215 (s, 1H); 6.993 (s, 1H); 3.079 (m, 1H); 2.480 (s, 3H); 2.439 (s) 3.002, 2.302 (s, 3H); 1.824-1.751 (m, 4H); 0.780-0.743 (m, 6H) ppm. MS, ES + = 315.2.

Example 7

Of 8- (1-ethyl-propyl) -2,6-dimethyl-3- (4-methyl-2-pyridin-2-yl-thiazol-5-yl) -imidazo [1,2-b] pyridazine Preparation

A. 8- (1-ethyl-propyl) -3- [2-bromo-4-methyl-5-thiazolyl] -2,6-dimethyl-imidazo [1,2-b] pyridazine in a 15 mL round bottom flask in an oven 0.028 g (0.089 mmol) of 8- (1-ethyl-propyl) -3- [4-methyl-5-thiazolyl] in 1.5 mL of dry CH₂Cl₂ dried and N₂ removed -2,6-Dimethyl-imidazo [1,2-b] pyridazine is cooled to 0 ° C. 0.019 g (0.107 mmol) of NBS is added and the reaction is stirred overnight until the solution is at room temperature. The reaction mixture is purified directly with hexane / ethyl acetate using chromatography as the solvent system. The product containing fractions are mixed to obtain 0.012 g (34% yield). MS (ES + = 395.1 (M + 1)); ¹H-NMR (DMSO-d₆) = 7.070 (s, 1H); 3.10 (m, 1H); 2.49 (s, 3H); 2.36 (s, 3H); 2.25 (s, 3H); 1.85-1.78 (m, 4H); 0.81-0.77 (m, 6H) ppm.

B. 8- (1-Ethyl-propyl) -2,6-dimethyl-3- (4-methyl-2-pyridin-2-yl-thiazol-5-yl) -imidazo [1,2-b] pyridazine 3- (2-Bromo-4-methyl-thiazol-5-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (380 mg, 0.96 mmol), 2-pyridine zinc bromide (0.5 M in THF, 2.1 mL, 4 mmol), Pz (PPh₃)₄ (30 mg, 0.026 mmol) and THF (3 mL) are heated at 80 ° C. for 18 hours. Add ethyl acetate (20 mL). The organic layer is separated, dried over magnesium sulfate, filtered and the solvent removed in vacuo. Purification is performed via silica gel chromatography using a 3: 1 mixture of hexane and ethyl acetate as eluent to give 325 mg (86%) of the title compound. ¹H-NMR (CDCl₃) δ 9.55 (m, 1H); 8.10 (m, 1H); 7.73 (m, 1H); 7.25 (m, 1H); 6.58 (s, 1H); 3.24 (m, 1H); 2.49 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 80 (t, 6H) ppm. MS / ES ⁺ = 391 (100%, M + 1).

Example 8

Preparation of 8- (1-ethyl-propyl) -3- [4-methyl-2- (3-pyridyl) -5-thiazolyl] -2,6-dimethyl-imidazo [1,2-b] pyridazine

To a microwave pressure tube, 0.070 g (0.178 mmol) of 8- (1-ethyl-propyl) -3- [2-bromo-4-methyl-5-thiazolyl] -2,6-dimethyl-imidazo [1,2-b] pyridazine, 0.066 g (0.534 mmol) pyridine-3-boronic acid, 0.103 g (0.089 mmol) Pd (PPh₃)₄, 0.257 mL (0.534 mmol) 2M aqueous. Of Na₂CO₃ and 1 mL 7: 3: 2 DME: H₂O: EtOH are added and the mixture is heated at 160 ° C. for 60 min. The reaction mixture is partitioned between 25 mL ethyl acetate and 25 mL water. The layers are separated and the aqueous phase is extracted with 3 × 25 mL of ethyl acetate, dried (MgSO₄) and concentrated in vacuo. The crude mixture is purified by chromatography using hexane / ethyl acetate as solvent system. The product containing fractions are mixed to give 0.045 g of product (64% yield). MS, ES + = 392.2 (M + 1); ¹H-NMR (DMSO-d₆) δ 9.16 (s, 1H); 8.65 (m, 1H); 8.34 (d, 1H); 7.60 (m, 7.06 (s, 1H); 3.06 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.34 (s, 3H); 1.87-1.82 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 9

Preparation of 8- (1-ethyl-propyl) -3- [4-methyl-2- (4-pyridyl) -5-thiazolyl] -2,6-dimethyl-imidazo [1,2-b] pyridazine

A similar procedure as Example 8 is used to produce the title compound in 10% yield from pyridine-4-boronic acid. MS (ES + = 392.3 (M + 1)); ¹H-NMR (DMSO-d₆) = 8.79 (s, 2H); 7.80 (m, 2H); 7.07 (s, 1H); 3.12 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.36 (s, 3H); 1.90-1.80 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 10

Preparation of 8- (1-ethyl-propyl) -3- [4-methyl-2- (thiophen-2-yl) -5-thiazolyl] -2,6-dimethyl-imidazo [1,2-b] pyridazine

Using a procedure similar to Example 8, the title compound is produced in 89% yield from thiophene-2-boronic acid. MS (ES + = 397.1 (M + 1)); ¹H-NMR (DMSO-d₆) = 7.81-7.79 (d, 1H); 7.78-7.77 (d, 1H); 21-7.20 (m, 1H); 7.05 (s, 1H); 3.19-3.15 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.27 (s, 3H); 1.85-1.83 (m, 4H); 0.82-0.79 (m, 6H) ppm.

Example 11

Preparation of 8- (1-ethyl-propyl) -3- [4-methyl-2- (2-fluorophenyl) -5-thiazolyl] -2,6-dimethyl-imidazo [1,2-b] pyridazine

Using a procedure similar to Example 8, the 82% yield of the title compound is produced from 2-fluorophenylboronic acid. MS (ES + = 409.2 (M + 1)); ¹H-NMR (DMSO-d₆) = 8.32-8.28 (m, 1H); 7.60-7.58 (m, 1H); 57-7.41 (m, 2H); 7.05 (s, 1H); 3.13-3.12 (m, 1H); 2.49 (s, 3H); 2.40 (s, 3H); 2.35 (s, 3H); 1.91-1.780 (m, 4H); 0.87-0.79 (m, 6H) ppm.

Example 12

Preparation of 8- (1-ethyl-propyl) -3- [4-methyl-2- (4-fluorophenyl) -5-thiazolyl] -2,6-dimethyl-imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 8, the crude compound is purified from 4-fluorophenylboronic acid by chromatography using 2% methanol in dichloromethane as the solvent system to give a 63% yield of the title compound. Generate. MS, ES + = 409.2 (M + 1); ¹H-NMR (DMSO-d₆) = 8.06-8.08 (m, 2H); 7.408-7.36 (m, 2H); 7.05 (s, 1H); 3.14-3.11 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.31 (s, 3H); 1.90-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 13

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 8, the 77% yield of the title compound is purified from 3-fluorophenylboronic acid by purification of the crude mixture by chromatography using 2% methanol in dichloromethane as the solvent system. Generate. MS, ES + = 409.2 (M + 1); ¹H-NMR (DMSO-d₆) = 7.84-7.78 (m, 2H); 7.64-7.57 (m, 2H); 7.41-7.36 (m, 1H); 7.06 (s, 1H); 3.15-3.11 (m, 1H); 2.45 (s, 3H); 2.40 (s, 3H); 2.32 (s, 3H); 1.91-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 14

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo [1,2-b] pyridazine

Using a procedure similar to Example 8, the 75% yield of the title compound is produced from 2,4-difluorophenylboronic acid. MS, ES + = 427.2 (M + 1); ¹H-NMR (DMSO-d₆) = 8.370-8.310 (m, 1H); 7.585-7.540 (m, 1H); 7.36-7.32 (m, 1H); 7.054 (s, 1H); 3.14-3.13 (m, 1H); 2.492 (s, 3H); 2.391 (s, 3H); 2.345 (s, 3H); 1.906-1.797 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Example 15

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(o-tolyl)-5-thiazolyl]-2,6-dimethyl-imidazo [1,2-b] pyridazine

Using a procedure similar to Example 8, the o-tolylboronic acid yielded the title compound in 87% yield, where the crude mixture was purified by silica gel chromatography using 2% methanol in dichloromethane as the solvent system. To do. MS, ES + = 405.2 (M + 1); ¹H-NMR (DMSO-d₆) = 7.857-7.838 (d, 1H); 7.429-7.419 (d, 2H); 7.393-7.352 (m, 1H); 7.049 (s, 1H); 3.145-3.114 (m, 1H); 2.647 (s, 3H); 2.592 (s, 3H); 2.406 (s, 3H); 2.337 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Example 16

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 8, the crude mixture was purified from 3,4-difluorophenylboronic acid by chromatography using 2% methanol in dichloromethane as the solvent system in 74% yield. A compound is produced. MS, ES + = 427.2 (M + 1); ¹H-NMR (DMSO-d₆) = 8.07-8.02 (m, 1H); 1.905-1.797 (m, 4H); 7.849 (7.66-7.59 (m, 1H); 7.062 (s, 1H); 3.12-3.11 (m, 1H); 2.498 (s, 3H); 2.392 (s, 3H); 2.319 (s, 3H); 0.826-0.790 (m, 6H) ppm.

Example 17

8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluoro-2-methylphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation of

Using a procedure similar to that in Example 8, 0.046 g of the title compound in 37% yield is produced from 4-fluoro-2-methylphenylboronic acid. MS, ES + = 423.2 (M + 1); ¹H-NMR (DMSO-d₆) = 7.918-7.882 (m, 1H); 7.323-7.241 (d, 1H); 7.234-7.192 (m, 1H); 7.049 (s, 1H); 3.142-3.111 (m, 1H); 2.650 (s, 3H); 2.499 (s, 3H); 2.401 (s, 3H); 2.330 (s, 3H); 1.905-1.779 (m, 4H); 0.969-0.788 (m, 6H) ppm.

Example 18

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-trifluoromethoxyphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo [1,2-b] pyridazine

To a microwave pressure tube, 0.100 g (0.254 mmol) of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo [1,2-b] pyridazine, 0.157 g (0.762 mmol) of 4-(trifluoromethoxy) benzenboronic acid, 0.147 g (0.127 mmol) of Pd(PPh₃)₄, 0.381 mL (0.762 mmol) of 2M aqueous sodium carbonate and 2 mL of ethanol are added. The reaction mixture is heated in the microwave at 150 ° C. for up to 1 hour. The reaction is partitioned between 50 mL ethyl acetate and 50 mL water. The layers are separated and the aqueous phase is extracted with 3 × 50 mL of ethyl acetate, dried (MgSO₄) and concentrated in vacuo. The crude mixture is purified by chromatography using 2% methanol in dichloromethane as the solvent system. The product containing fractions are mixed to obtain 0.085 g of product with a yield of 70%. MS (ES + = 475.2 (M + 1)); ¹H-NMR (DMSO-d₆) = 8.134-8.112 (d, 2H); 7.853-7.532 (d, 2H); 0.59 (s, 1H); 3.142-3.113 (m, 1H); 2.500 (s, 3H); 2.399 (s, 3H); 2.330 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Example 19

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiophen-3-yl)-imidazo [1,2-b] pyridazine

A. 4,4,5,5-Tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2] dioxaborolane A 250 mL round bottom flask was charged with 3-bromo- in DMSO (85 mL), 4-Methyl-thiophene (5.00 g, 28.24 mmol), bis (pinacolate) diboron (7.89 g, 31.06 mmol) and KOAc (8.32 g, 84.72 mmol) are added. The mixture is degassed by N₂ bubbling for 5 minutes, PdCl₂(dppf)₂ * CH₂Cl₂ (1.15 g, 1.42 mmol) is added and the reaction is heated and stirred at 85 ° C. overnight. The reaction is cooled to rt, diluted with EtOAc (400 mL), washed with H₂O (3 × 300 mL), dried over MgSO₄, filtered and concentrated. Purify the crude material by chromatography to give the title compound (3.69 g, 16.5 mmol, 58%). ES-MS (m/z): calcd ^{C₂₁H₂₇N₃S} (M +); 224.1; ANALYSIS: 224.9.

B. 4-Methyl-3-thiopheneboronic acid 4,4,5,5-tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2] dioxaborolane (3.69 g, 16.47 mmol) is treated with H₂O (30 mL) and then with NaOH (7.05 g, 32.95 mmol). The resulting mixture is stirred overnight at room temperature. The organic solvent is removed in vacuo. The remaining amount was diluted with H₂O (50 mL) and extracted with EtOAc (2 × 100 mL). Combine the organic extracts, dry over Na₂SO₄, filter and concentrate. Purification of the crude material by chromatography gives the title compound (0.82 g, 5.78 mmol, 35%). ¹H NMR (CDCl₃) : δ 1.33 (s, 3H) 2.64-2.66 (m, 2H) 7.00-7.02 (m, 1H) 8.27 (d (J = 3.0 Hz, 1H)). ES-MS (m/z): Calcd ^{C₂₁H₂₇N₃S} (MH)⁺: 141.0; ANALYSIS: 141.1.

C. 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiophen-3-yl)-imidazo [1,2-b] pyridazine 4-methyl-3-thiopheneboronic acid (0.27- (1.91 mmol) and 20-mL stock solution (DME: H₂O: EtOH = 7: 3: 2) 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo To a 100 mL round bottom flask containing [1,2-b] pyridazine (0.65 g, 1.91 mmol) is added 2M Na₂CO₃ (1.9 mL). The resulting mixture is degassed by N₂ bubbling for 5 minutes. Pd(PPh₃)₄ (0.11 g, 0.096 mmol) is then added. The reaction mixture is refluxed overnight. The reaction was diluted with H₂O (20 mL), extracted with EtOAc (3 × 30 mL), dried (Na₂SO₄), filtered and the crude material was purified by chromatography to give the title compound (0.52 g, 1.66 mmol, 87%). ¹H NMR (CDCl₃) : δ 0.89 (t (J = 7.5 Hz, 6H)) 1.75-1.90 (m, 4H) 2.13 (d, 0.8 Hz J = 3H) 2.44 (s, 3H) 2.49 (s, 3H) 3.30-3.39 (m, 1H) 6.64 (s, 1H) 7.08-7.11 (m, 1H) 8.4 (d (J = 3.1 Hz, 1H)). ES-MS (m/z): calcd ^{C₂₃H₂₉N₃S} (M + H)⁺: 314.5; ANALYSIS: 314.2.

Example 20

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo [1,2-b] pyridazine

8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine (12.0 g, 34.96 mmol) and PdCl₂(dppf) (1.28 g) To a mixture of 1.75 mmol) is added a 0.5 M solution of 3-methyl-2-thienyl zinc bromide in THF (100 mL, 50.0 mmol). The mixture was stirred overnight at 65 ° C., diluted with EtOAc (500 mL), washed with 10% citric acid (500 mL), water (400 mL), brine (400 mL), dried over MgSO₄, filtered and concentrated. To do. Purify the residue with ISCO (10% to 20% EtOAc / hexanes gradient) to give the

title compound (8.83 g, 28.17 mmol, 81%). $^1\text{H NMR}$ (CDCl_3): δ 0.92 (t, J = 7.4 Hz, 6H), 1.78-1.95 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.33-3.43 (m, 1H), 6.69 (s, 1H), 7.06 (d, J = 4.9 Hz, 1H), 7.46 (d, J = 4.9 Hz, 1H). LC / MS (m/z): calcd $[\text{C}_{15}\text{H}_{19}\text{N}_4\text{O}_2]$ (M + H) $^+$: 314.6; ANALYSIS: 314.2.

Example 21

Preparation of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo [1,2-b] pyridazine (8.83 g, 28.17 mmol) and CH₃Cl (90 mL), is added NBS (5.26g, 29.58 mmol). The solution is stirred at ambient temperature for 2 hours. The solution is washed with water (3 x 75 mL), dried over MgSO₄, filtered and concentrated to give the title compound (10.5 g, 26.75 mmol, 95%). $^1\text{H NMR}$ (CDCl_3): δ 0.87 (t, J = 7.3 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.51 (s, 3H), 3.25-3.36 (m, 1H), 6.68 (s, 1H), 6.93 (d, J = 4.9 Hz, 1H) ppm. LC / MS (m/z): calcd $[\text{C}_{15}\text{H}_{19}\text{N}_4\text{O}_2]$ (M + H) $^+$: 392.6; ANALYSIS: 392.1, 394.1.

Example 22

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophene-2-carboxylic acid methyl ester
CH₃OH (12 mL) solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] A solution of pyridazine (1.00 g, 2.66 mmol), DMSO (18 mL), Et₃N (2.0 mL) with Pd(OAc)₂ (0.12 g, 0.538 mmol), dppf (0.937 g, 1.69 mmol) react with CO medium (100 psi) at 80 °C. for 24 hours. The reaction is diluted with EtOAc (200 mL), washed with 0.1 M HCl (2 x 50 mL), brine (50 mL), dried over Na₂SO₄, filtered through silica gel and extracted with excess EtOAc. Purification of the crude material by chromatography gives the title compound (0.79 g, 2.12 mmol, 80%). $^1\text{H NMR}$ (CDCl_3): δ 0.89 (t, J = 7.7 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.32-3.42 (m, 1H), 3.91 (s, 3H), 6.72 (s, 1H), 7.73 (s, 1H). ES-MS (m/z): calcd $[\text{C}_{20}\text{H}_{25}\text{N}_4\text{O}_3]$ (M + H) $^+$: 372.5; ANALYSIS: 372.2.

Example 23

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophene-2-carboxylic acid methylamide
A. 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophene-2-carboxylic acid in CH₃OH (10 mL) Of (1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophene-2-carboxylic acid methyl ester (0.78 g, 2.10 mmol) is treated with 5.0 M NaOH (2.1 mL, 10.5 mmol). The resulting reaction mixture is refluxed for 4 hours. The organic solvent is removed in vacuo and the aqueous residue is acidified by adding 2.0 M HCl at pH 5-6, then extracted with EtOAc (3 x 50 mL) and dried (Na₂SO₄). Filter and concentrate to give the title compound (0.74 g, 2.07 mmol, 98%). $^1\text{H NMR}$ (DMSO-d_6): δ 0.79 (t, J = 7.6 Hz, 6H), 1.75-1.86 (m, 4H), 2.05 (s, 3H), 3.5 (s, 3H), 2.47 (s, 3H), 3.66-3.14 (m, 1H), 7.01 (s, 1H), 7.68 (s, 1H), 13.1 (Bs, 1H). ES-MS (m/z): calcd $[\text{C}_{20}\text{H}_{25}\text{N}_4\text{O}_3]$ (M + H) $^+$: 358.5; ANALYSIS: 358.2.
B. 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophene-2-carboxylic acid methylamide 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophene-2-carboxylic acid (0.17 g, 0.47 mmol) at room temperature. React with 2.0 M oxalyl chloride in CH₂Cl₂ (3.0 mL) for 1 hour. Excess reagent and solvent are removed in vacuo. The residue is dissolved in CH₂Cl₂ (3 mL), cooled to 0 °C. and treated with 2.0 M methylamine in THF (3 mL). The reaction is stirred at 0 °C. for 10 minutes and at room temperature for 30 minutes. The reaction is diluted with EtOAc (50 mL), washed with H₂O (15 mL), 0.1 M NaOH (2 x 50 mL), dried (Na₂SO₄), filtered and concentrated. The material is purified to give the title compound (0.91 g, 0.25 mmol, 53%). $^1\text{H NMR}$ (CDCl_3): δ 0.89 (t, J = 7.2 Hz, 6H), 7.5-1.91 (m, 4H), 2.14 (s, 3H), 2.47 (s, 3H), 2.52 (s, 3H), 3.02 (d, J = 4.8 Hz, 3H), 3.28-3.36 (m, 1H), 5.90-6.01 (m, 1H), 6.69 (s, 1H), 7.43 (s, 1H). ES-MS (m/z): calcd $[\text{C}_{20}\text{H}_{25}\text{N}_4\text{O}_3]$ (M + H) $^+$: 371.5; analysis value: 371.2.

Example 24

8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-1H-imidazol-2-yl)-thiophen-2-yl]-imidazo [1,2-b] pyridazine
3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo-[1,2-b] pyridazine in DMF (50 mL) (0.98 g, 2.51 mmol) and 1-methyl-1H-imidazole (0.2 mL), Pd(OAc)₂ (34 mg, 0.15 mmol), PPh₃ (79 mg, 0.299 mmol), Cs₂CO₃ (1.95 g, 6.0 mmol) is stirred overnight at 130-140 °C. under N₂. The reaction mixture is cooled, diluted with EtOAc (300 mL), washed with H₂O (3 x 100 mL), dried (Na₂SO₄), filtered and concentrated. Purification of the crude material obtained by chromatography gives the title compound (0.51 g, 1.29 mmol, 51%). $^1\text{H NMR}$ (CDCl_3): δ 0.89 (t, J = 7.5 Hz, 6H), 1.77-1.92 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.54 (s, 3H), 3.30-3.40 (m, 1H), 3.81 (s, 3H), 6.69 (s, 1H), 7.02 (s, 1H), 7.24 (s, 1H), 7.52 (s, 1H). ES-MS (m/z): calcd $[\text{C}_{22}\text{H}_{27}\text{N}_6]$ (M + H) $^+$: 394.6; ANALYSIS: 394.3.

Example 25

8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-imidazo [1,2-b] pyridazine
A solution of 1-methyl-1,2,4-triazole (0.15 mL, 2.04 mmol) at -78 °C. and THF (3 mL) was added n-Bu in hexane (1.63 mL, 2.14 mmol). Add to a 1.34M solution of 4-Li over 20 minutes, then stir at -78 °C for 1.5 hours. A 0.5 M solution of ZnCl₂ in THF (4.28 mL, 2.14 mmol) is added and the solution is heated to ambient temperature. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.019 mmol) and PdCl₂(dppf) (0.037 g, 0.051 mmol) are added and the solution is heated at 65 °C. overnight and diluted with CH₂Cl₂ (30 mL). The organic layer is washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO (20% to 60% EtOAc / hexane gradient). The residue was dissolved in Et₂O, treated with Darco®-60 for 15 minutes, dried over Na₂SO₄ and filtered to give the title compound (0.24 g, 0.61 mmol, 60%). obtain. $^1\text{H NMR}$ (CDCl_3): δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.29 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.37 (m, 1H), 4.14 (s, 3H), 6.69 (s, 1H), 7.45 (s, 1H), 7.87 (s, 1H). LC / MS (m/z): calcd $[\text{C}_{21}\text{H}_{26}\text{N}_5\text{S}]$ (M + H) $^+$: 395.6; ANALYSIS: 395.2.

Example 26

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophene-2-carbonitrile
3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.50 g, 1.28 mmol), DMF (5 mL) and Zn (CN)₂ (0.090 g, 0.76 mmol) are degassed with nitrogen for 15 min. Pd(PPh₃)₄ (0.74 g, 0.064 mmol) and the solution are heated at 100 °C. overnight. The solution is diluted with EtOAc (50 mL), washed with 2M NH₄OH (2 x 50 mL), brine (30 mL), dried over MgSO₄, filtered and concentrated. Purify by ISCO column chromatography (15% to 20% EtOAc / hexane gradient) to give the title compound (0.39 g, 1.15 mmol, 91%). $^1\text{H NMR}$ (CDCl_3): δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.15 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 3.25-3.34 (m, 1H), 6.72 (s, 1H), 7.53 (s, 1H). LC / MS (m/z): Calculated value $[\text{C}_{19}\text{H}_{22}\text{N}_4\text{S}]$ (M + H) $^+$: 339.6, Anal. Value: 339.2.

Example 27

(2-(5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophen-2-yl)-pyro-Ru-1-yl)-dimethyl-amine preparation
To a solution of 1-(dimethylamino)-pyrrole (0.24 mL, 2.04 mmol) at 0 °C. and THF (4 mL) is added 1.24 M n-BuLi (1.73 mL, 2.14 mmol). The solution is warmed to

ambient temperature and stirred for 2 hours. 0.5M ZnCl₂ (4.28 mL, 2.14 mmol) is added and the solution is stirred for 1 hour. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol) and PdCl₂ (dppf) (0.037 g, 0.051 mmol) are added and the solution is heated at 65 ° C. overnight. The solution is diluted with EtOAc (30 mL), washed with saturated NH₄Cl (30 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% to 20% EtOAc gradient) to give the title compound (0.41 g, 0.97 mmol, 95%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.11 (s, 3H), 2.51 (s, 6H), 2.83 (s, 6H), 3.29-3.39 (m, 1H), 6.18-6.21 (m, 1H), 6.35 (dd, J = 4.0, 1.8 Hz, 1H), 6.65 (s, 1H), 6.98 (dd, J = 4.0, 1.8 Hz, 1H), 7.25 (s, 1H). LC / MS (m / z): calcd [M + H]⁺: 422.2; ANALYSIS: 422.4.

Examples 28 and 29

8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(2-methyl-2,5-dihydro-1H-tetrazol-5-yl)-thiophen-2-yl)-imidazo [1,2-b] pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(1-methyl-1H-tetrazol-5-yl)-thiophen-2-yl)-imidazo [1,2-b] pyridazine

Example 28

Example 29

A. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(1H-tetrazol-5-yl)-thiophen-2-yl)-imidazo [1,2-b] pyridazine 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophene-2-carbonitrile (0.25 g, 0.74 mmol) and DMF (2.5 mL) are added. Et₃N·HCl (0.31 g, 2.22 mmol) and NaN₃ (0.14 g, 2.20 mmol). The solution is heated at 100 ° C. overnight. The solution is diluted with water (20 mL) and extracted with EtOAc (3 × 15 mL) and the combined organic layers are washed with 0.1 M HCl (20 mL), water (20 mL), brine (20 mL) and dried over MgSO₄. Filter and concentrate. The residue is recrystallized from acetonitrile to give the title compound (0.14 g, 0.37 mmol, 50%). ¹H NMR (CDCl₃) δ 0.81 (t, J = 7.5 Hz, 6H), 1.66-1.87 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.26-3.35 (m, 1H), 6.53 (s, 1H), 7.64 (s, 1H). LC / MS (m / z): calcd [M + H]⁺: 382.6; ANALYSIS: 382.2.

B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(2-methyl-2,5-dihydro-1H-tetrazol-5-yl)-thiophen-2-yl)-imidazo [1,2-b] pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(1-methyl-1H-tetrazol-5-yl)-thiophen-2-yl)-imidazo [1,2-b] pyridazine 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(1H-tetrazol-5-yl)-thiophen-2-yl)-imidazo [1,2-b] pyridazine (0.14 g, 0.35 mmol) and THF (5 mL), Et₃N (0.1 mL, 0.71 mmol) and MeI (0.024 mL, 0.39 mmol) is added. The solution is stirred overnight, diluted with EtOAc (20 mL), washed with water (15 mL), 0.1 M HCl (15 mL), brine (15 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by ISCO column chromatography (20% to 40% EtOAc / hexane gradient) to give Example 28 (0.71 g, 0.18 mmol, 51%) and Example 29 (0.031 g, 0.078 mmol, 22 %).

Example 28. ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.92 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.38 (m, 1H), 4.38 (s, 3H), 6.68 (s, 1H), 7.71 (s, 1H). LC / MS (m / z): calcd [M + H]⁺: 396.6; ANALYSIS: 396.3.

Example 29. ¹H NMR (CDCl₃) δ 0.89 (t, J = 7.4 Hz, 6H), 1.73-1.94 (m, 4H), 2.23 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.37 (m, 1H), 4.30 (s, 3H), 6.62 (s, 1H), 7.63 (s, 1H). LC / MS (m / z): calcd [M + H]⁺: 396.6; ANALYSIS: 396.3.

Example 30

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-4-yl-thiophen-2-yl)-imidazo [1,2-b] pyridazine

A. 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (1.20 g, 3.06 mmol) and THF (10 mL) is added dropwise to a -78 ° C. solution of 1.30 M n-Bu-Li (2.47 mL, 3.21 mmol). The solution is stirred at -78 ° C. for 1 hour. B(OMe)₃ (0.38 mL, 3.65 mmol) is added, the solution is warmed to ambient temperature and stirred for 2 h. 1 M HCl is added, the solution is stirred for 10 min, CH₂Cl₂ (2 × 30 mL). Extracted with, dried over MgSO₄, filtered and concentrated to give the title compound (0.47 g, 1.32 mmol, 43%). ¹H NMR (CDCl₃) δ 0.92 (t, J = 7.5 Hz, 6H), 1.71-1.98 (m, 4H), 2.02 (s, 3H), 2.64 (s, 3H), 2.69 (s, 3H), 3.64-3.83 (m, 1H), 7.06 (d, J = 5.3 Hz, 1H), 7.54 (d, J = 5.3 Hz, 1H), 7.20 (s, 1H). LC / MS (m / z): Calculated C₁₈H₂₄BN₃O₂S [M + H]⁺: 358.4; Analytical value: 358.2.

B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-4-yl-thiophen-2-yl)-imidazo [1,2-b] pyridazine 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25 g, 0.70 mmol), 4-bromopyridine hydrochloride (0.16 g, 0.84 mmol) and a solution of 2M Na₂CO₃ (0.87 mL, 1.75 mmol) and n-PrOH (2.5 mL) with nitrogen for 10 min. Gas. Pd(PPh₃)₄ (0.040 g, 0.035 mmol) is added and the solution is heated at 85 ° C. overnight. The solution is diluted with CH₂Cl₂ (40 mL), washed with 10% Na₂CO₃ (30 mL), water (30 mL), brine (30 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (20% to 40% EtOAc / hexane gradient) to give the title compound (0.16 g, 0.41 mmol, 59%). ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.43 (s, 1H), 7.52 (d, J = 5.5 Hz, 2H), 8.62 (d, J = 5.5 Hz, 2H). LC / MS (m / z): calcd [M + H]⁺: 391.2 ANALYSIS: 391.2.

Example 31

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-3-yl-thiophen-2-yl)-imidazo [1,2-b] pyridazine

3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.50 g, 1.02 mmol) and THF (5 mL) is added. 1.34 M n-Bu-Li (1.9 mL, 1.34 mmol). The solution is stirred at -78 ° C. for 30 minutes and 0.5 M ZnCl₂ in THF (2.7 mL, 1.34 mmol) is added to warm the solution to ambient temperature. After 30 minutes, 3-bromopyridine (0.15 mL, 1.53 mmol) and PdCl₂ (dppf) (0.047 g, 0.064 mmol) are added and the solution is heated at 65 ° C. overnight. The solution is diluted with CH₂Cl₂ (40 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by ISCO column chromatography (EtOAc / hexanes gradient 20% to 40%), concentrated, redissolved in Et₂O. The solution was treated with Darco®-60 for 15 minutes, dried over Na₂SO₄ and filtered through Celite® to give the title compound (0.26 g, 0.57 mmol, 52%). obtain. ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.26-7.32 (m, 2H), 7.86 (dt, J = 7.9, 1.8 Hz, 1H), 8.59 (d, J = 3.2 Hz, 1H), 8.89 (s, 1H). LC / MS (m / z): calcd [M + H]⁺: 391.6; ANALYSIS: 391.2.

Example 32

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo [1,2-b] pyridazine

3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.50 g, 1.02 mmol) and PdCl₂ (dppf) (0.047 g, 0.064 mmol) is added a 0.5 M solution of 2-pyridylzinc bromide in THF (5.1 mL, 2.55 mmol). The mixture was stirred overnight at 65 ° C., diluted with EtOAc (50 mL), washed with 10% citric acid (50 mL), water (40 mL), brine (40 mL), dried over MgSO₄, filtered and concentrated. To do. The residue is purified by ISCO column chromatography (20% to 40% EtOAc / hexane gradient) to give the title compound (0.45 g, 1.15 mmol, 89%). ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H),

2.52 (s, 6H), 3.30-3.39 (m, 1H), 6.67 (s, 1H), 7.12-7.16 (m, 1H), 7.53 (s, 1H), 7.63-7.71 (m, 2H), 8.57 (dt, J = 1.3, 4.8 Hz, 1H). LC / MS (m / z) : calcd $\text{C}_{22}\text{H}_{26}\text{N}_4\text{S}$ (M + H) + : 391.5; ANALYSIS: 391.2.

Example 33

Of 8- (1-ethyl-propyl) -2,6-dimethyl-3- (3-methyl-5-pyridin-2-yl-thiophen-2-yl) -imidazo [1,2-b] pyridazine hydrochloride Preparation
8- (1-Ethyl-propyl) -2,6-dimethyl-3- (3-methyl-5-pyridin-2-yl-thiophen-2-yl) -imidazo [1,2-b] pyridazine (0.028 mL, 0.39 mmol) is added to a solution of 15 g, 38 mmol) and MeOH (2 mL). After 1 hour, the solution is concentrated and the residue is recrystallized from EtOAc / hexanes to give the title compound (0.11 g, 0.26 mmol, 69%). ^1H NMR (CDCl_3) : δ 0.97 (t, J = 7.4 Hz, 6H), 1.75-2.03 (m, 4H), 2.17 (s, 3H), 2.66 (s, 3H), 2.77 (s, 3H), 3.86-3.98 (m, 1H), 7.17 (s, 1H), 7.21-7.30 (m, 2H), 7.62 (bs, 1H), 7.67-7.72 (m, 2H), 8.60 (d, J = 4.8 Hz, 1H). LC / MS (m / z) : calcd $\text{C}_{22}\text{H}_{26}\text{N}_4\text{S}$ (M + H) + : 428.1; ANALYSIS: 391.2.

Example 34

8- (1-Ethyl-propyl) -2,6-dimethyl-3- (3-methyl-5- (2-methyl-2H-pyrazol-3-yl) -thiophen-2-yl) -imidazo [1,2-b] pyridazine Preparation
Using a procedure similar to that in Example 25, 1-methylpyrazole (0.17 g, 2.04 mmol), 1.56M n-Bu-Li (1.34 mL, 2.09 mmol) ZnCl_2 (4.3 mL, 2.14 mmol), 3- (5-Bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.037 g, 0.051 mmol) afford the title compound (0.35 g, 0.89 mmol, 88%). ^1H NMR (CDCl_3) : δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 4.65 (s, 3H), 6.42 (d, J = 1.8 Hz, 1H), 6.58 (s, 1H), 7.08 (s, 1H), 7.46 (d, J = 1.8 Hz, 1H). LC / MS (m / z) : calcd $\text{C}_{27}\text{H}_{32}\text{N}_6\text{S}$ (M + H) + : 394.7; ANALYSIS: 394.2.

Example 35

Of 8- (1-ethyl-propyl) -2,6-dimethyl-3- (3-methyl-5-thiazol-4-yl-thiophen-2-yl) -imidazo [1,2-b] pyridazine Preparation
Using a procedure similar to that in Example 31, 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol), 1.34M n-Bu-Li (0.8 mL, 1.07 mmol), THF (2.14 mL, 1.07 mmol) 0.5M ZnCl_2 in 4-bromo-thiazol (0.20 mL, 1.22 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.037 g, 0.051 mmol) give the title compound (0.16 g, 0.40 mmol, 40%). ^1H NMR (CDCl_3) : δ 0.92 (t, J = 7.4 Hz, 6H), 1.70-1.95 (m, 4H), 2.17 (s, 3H), 2.54 (s, 3H), 2.56 (s, 3H), 3.38-3.48 (m, 1H), 7.16 (d, J = 1.8 Hz, 1H), 7.44 (s, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H). LC / MS (m / z) : calcd $\text{C}_{19}\text{H}_{20}\text{N}_4\text{S}_2$ (M + H) + : 397.7; ANALYSIS: 397.2.

Example 36

8- (1-Ethyl-propyl) -2,6-dimethyl-3- (3-methyl-5- (6-methyl-pyridin-2-yl) -thiophen-2-yl) -imidazo [1,2-b] pyridazine Preparation
Using a procedure similar to that in Example 32, 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.60 g, 1.53 mmol) and, $\text{PdCl}_2(\text{dppf})$ (0.056 g, 0.076 mmol) and THF (5.0 mL, 3.06 mmol) solution of 6-methyl-2-pyridyl zinc A 0.5 M solution of bromide gives the title compound (0.29 g, 0.72 mmol, 47%). ^1H NMR (CDCl_3) : δ 0.89 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 2.58 (s, 3H), 3.31-3.43 (m, 1H), 6.67 (s, 1H), 7.00 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 8.56 (t, J = 7.7 Hz, 1H). LC / MS (m / z) : calcd $\text{C}_{20}\text{H}_{22}\text{N}_4$ (M + H) + : 405.7; ANALYSIS: 405.2.

Example 37

Preparation of 8- (1-ethyl-propyl) -2,6-dimethyl-3- (3-methyl-5-phenyl-thiophen-2-yl) -imidazo [1,2-b] pyridazine
Using a procedure similar to that in Example 32, 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.50 g, 1.27 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.056 g, 0.069 mmol) and THF (5.5 mL, 2.76 mmol) solution of 0.5M phenyl zinc iodides in Gives the title compound (0.25 g, 0.64 mmol, 50%). ^1H NMR (CDCl_3) : δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.41 (m, 1H), 6.68 (s, 1H), 7.26 (s, 1H), 7.27-7.30 (m, 1H), 7.35-7.41 (m, 2H), 7.61-7.66 (m, 2H). LC / MS (m / z) : calcd $\text{C}_{24}\text{H}_{26}\text{N}_4\text{S}$ (M + H) + : 390.3; ANALYSIS: 390.3.

Example 38

Of 8- (1-ethyl-propyl) -3- (5- (3-fluoro-phenyl) -3-methyl-thiophen-2-yl) -2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation
Using a procedure similar to that in Example 32, 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.50 g, 1.27 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.047 g, 0.063 mmol) and 0 THF (5.1 mL, 2.55 mmol) in 3-fluorophenyl zinc iodides. The title compound (0.24 g, 0.59 mmol, 46%) is produced from a 5M solution. ^1H NMR (CDCl_3) : δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.31-3.39 (m, 1H), 6.69 (s, 1H), 6.94-7.01 (m, 1H), 7.26 (s, 1H), 7.30-7.42 (m, 3H). LC / MS (m / z) : calcd $\text{C}_{24}\text{H}_{26}\text{FN}_4\text{S}$ (M + H) + : 408.7; ANALYSIS: 408.2.

Example 39

Of 8- (1-ethyl-propyl) -3- (5- (4-fluoro-phenyl) -3-methyl-thiophen-2-yl) -2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation
A slurry of 0.05 g / mL Resin@ Zn and 1-bromo-4-fluoro-benzene (0.29 mL, 2.68 mmol) in THF (0.25 g, 4.01 mmol) were refluxed overnight. Heat. The solution is filtered under nitrogen. 3- (5-Bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.35 g, 0.89 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.033 g, 0.045 mmol) were added and the solution was heated at reflux overnight, diluted with EtOAc (30 mL), 10% citric acid (20 mL), water (20 mL). Washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (10% to 15% EtOAc / hexane gradient) to yield the title compound (0.091 g, 0.22 mmol, 25%). ^1H NMR (CDCl_3) : δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.38 (m, 1H), 6.68 (s, 1H), 7.06 (d, J = 8.8 Hz, 2H), 7.18 (s, 1H), 7.59 (dd, J = 8.5, 5.3 Hz, 2H). LC / MS (m / z) : calcd $\text{C}_{24}\text{H}_{26}\text{FN}_4\text{S}$ (M + H) + : 408.7; ANALYSIS: 408.3.

Example 40

8- (1-Ethyl-propyl) -2,6-dimethyl-3- (3-ethyl-5- (6-methyl-pyridin-2-yl) -thiophen-2-yl) -imidazo [1,2-b] pyridazine Preparation
Using a procedure similar to that in Example 31, 2-bromo-6-ethylpyridine (0.26 g, 1.41 mmol), 1.56 M n-Bu-Li (0.94 mL, 1.47 mmol), THF (3.0 mL, 0.5M ZnCl_2 in 1.53 mmol), 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.50 g, 1.27 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.047 g, 0.064 mmol) yield the title compound (0.15 g, 0.36 mmol, 28%). To do. ^1H NMR (CDCl_3) : δ 0.90 (t, J = 7.5 Hz, 6H), 1.34 (t, J = 7.5 Hz, 3H), 1.75-1.94 (m, 4H), 2.16 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 2.85 (q, J = 16.2, 7.5 Hz, 2H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.53 (s, 1H), 8.59 (t, J = 7.8 Hz, 1H). LC / MS (m / z) : calcd $\text{C}_{25}\text{H}_{30}\text{N}_4$ (M + H) + : 419.3; ANALYSIS: 419.3.

Example 41

8- (1-Ethyl-propyl) -2,6-dimethyl-3- (3-methyl-5- (6-methyl-pyridin-2-yl) -thiophen-2-yl) -imidazo [1,2-b] pyridazine Preparation of pyridazine hydrochloride
Using a procedure analogous to that in Example 33, 8- (1-ethyl-propyl) -2,6-dimethyl-3- (3-methyl-5- (6-methyl-pyridin-2-yl) -thiophen-2-yl) -imidazo [1,2-b] pyridazine (0.55

g, 1.36 mmol) from MeOH (6 mL) and AcCl (0.098 mL, 1.36 mmol) gave the title compound (0.11 g, 0.25 mmol, 42%). ¹H NMR (CDCl₃), δ 0.96 (t, J = 7.2 Hz, 6H), 1.74-1.89 (m, 2H), 1.89-2.02 (m, 2H), 2.22 (s, 3H), 2.68 (s, 3H), 2.78 (s, 3H), 3.08 (s, 3H), 3.88-3.98 (m, 1H), 7.23 (s, 1H), 7.40 (d, J = 6.9 Hz, 1H), 7.71 (d, J = 4.8 Hz, 1H), 8.06 (s, 1H), 8.82 (s, 1H). LC / MS (m/z): calcd (M + H)⁺: 441.3; ANALYSIS: 405.2.

Example 42

Of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-thiazol-2-yl-thiophen-2-yl)-imidazo [1,2-b] pyridazine Preparation

Using a procedure similar to that in Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.46 g, 1.17 mmol), from THF (4.7 mL, 2.35 mmol) in 0.5 M 2-thiazolyl zinc bromide and PdCl₂ (dppf) (0.043 g, 0.059 mmol) To yield the title compound (0.32 g, 0.81 mmol, 70%). ¹H NMR (CDCl₃), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 7.70 (s, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.47 (s, 1H), 7.78 (d, J = 3.6 Hz, 1H). LC / MS (m/z): calcd (M + H)⁺: 397.7; ANALYSIS: 397.1.

Example 43

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrazin-2-yl-thiophen-2-yl)-imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol) (Example wrap-2), 2-chloropyridazine (0.11 mL, 1.22 mmol), 1.42 M n-BuLi (1.52 mL, 1.07 mmol), 0.5 M ZnCl₂ and PdCl₂ (dppf) (0.037 g, 0.051 mmol) in THF (2.14 mL, 1.07 mmol) to give the title compound (0.19 g, 0.49 mmol, 48%) is generated. ¹H NMR (CDCl₃), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.20 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.53 (s, 1H), 8.40 (d, J = 2.6 Hz, 1H), 8.51 (t, J = 1.9 Hz, 1H), 8.96 (d, J = 0.9 Hz, 1H). LC / MS (m/z): calcd (M + H)⁺: 392.3; ANALYSIS: 392.2.

Example 44

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-[2,2']bithiophenyl-5-yl)-imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.76 mmol), THF (3.0 mL, 1.53 mmol) in 0.5 M 2-thiophenyl zinc bromide and PdCl₂ (dppf) (0.029 g, 0.038 mmol) from To yield the title compound (0.25 g, 0.63 mmol, 83%). ¹H NMR (CDCl₃), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.14 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.02 (dd, J = 5.0, 3.5 Hz, 1H), 7.11 (s, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.19 (dd, J = 5.0, 1.0 Hz, 1H). LC / MS (m/z): calcd (M + H)⁺: 396.7; ANALYSIS: 396.2.

Example 45

Preparation of 3-(5-butyl-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 25, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol), 1.34 M n-BuLi (1.60 mL, 2.14 mmol), 0.5 M ZnCl₂ (4.3 mL, 2.14 mmol) and PdCl₂ (dppf) (0.037 g, 0.051 mmol) produces the title compound (0.25 g, 0.69 mmol, 68%). ¹H NMR (CDCl₃), δ 0.88 (t, J = 7.5 Hz, 6H), 0.97 (t, J = 7.5 Hz, 3H), 1.40-1.51 (m, 2H), 1.67-1.92 (m, 6H), 2.07 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 3.30-3.38 (m, 1H), 6.64 (s, 1H), 6.70 (s, 1H). LC / MS (m/z): Calculation The value (M + H)⁺: 370.3; ANALYSIS: 370.2.

Example 46

8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-1H-pyrazol-3-yl)-thiophen-2-yl]-imidazo [1,2-b] pyridazine Preparation of 1,2-b] pyridazine

Using a procedure similar to that in Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol), 1.42 M n-BuLi (0.75 mL, 1.07 mmol), 0.5 M ZnCl₂ in THF (2.14 mL, 1.07 mmol), 3-Bromo-1-methyl-1H-pyrazole (Pavlik, J., Kurzweil, E., J. Org. Chem., 1991, 56, 22, 6313) (0.20 g, 1.22 mmol) and PdCl₂ (dppf) (0.037 g, 0.051 mmol) produces the title compound (0.041 g, 0.10 mmol, 10%). ¹H NMR (CDCl₃), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 3.95 (s, 3H), 6.47 (d, J = 2.2 Hz, 1H), 6.67 (s, 1H), 7.25 (s, 1H), 7.36 (d, J = 2.2 Hz, 1H). LC / MS (m/z): Calculated (M + H)⁺: 394.3; ANALYSIS: 394.2.

Example 47

8-(1-ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiazol-5-yl]-thiazol-5-yl]-imidazo [1,2-b] pyridazine Preparation of 1,2-b] pyridazine

82 mg 1-methyl-1,2,4-triazole (0.99 mmol) was dissolved in 2 mL dry THF, cooled to -78 °C, and 0.4 mL n-hexane (0.99 mmol). Add butyl lithium 2.5M. The reaction is stirred from -78 °C to room temperature for 10 minutes and cooled again to -78 °C. To 1.98 mL of 0.5 M zinc chloride, add a 0.5 M solution in THF (0.99 mmol) and stir from -78 °C to room temperature for 15 minutes. 265 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.66 mmol) and 27 mg of PdCl₂ (dppf) (0.033 mmol) are added, the vial is covered with a Teflon cap and heated at 80 °C for 2 days. The reaction is cooled to room temperature, quenched with saturated NH₄Cl and extracted with CH₂Cl₂. The separated CH₂Cl₂ layer is dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel chromatography column (hexane: AcOEt: 2M NH₃ in MeOH = 10: 2: 1) to give 57 mg of the title product. Yield 22%; Mass spectrum (m/e): 396 (M + 1)⁺ ¹H-NMR (CDCl₃), δ 7.96 (s, 1H), 6.77 (s, 1H), 4.45 (s, 3H), 3.36 (m, 1H), 2.55 (s, 3H), 2.52 (s, 3H), 2.47 (s, 3H), 1.88 (m, 4H), 0.92 (t, J = 7.3 Hz, 6H).

Example 48

3-(4-Bromo-2-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation of 1,2-b] pyridazine

82 mg 1-methyl-1,2,4-triazole (0.99 mmol) was dissolved in 2 mL dry THF, cooled to -78 °C, and 0.4 mL n-hexane (0.99 mmol). Add butyl lithium 2.5M. The reaction is stirred from -78 °C to room temperature over 10 minutes and cooled again to -78 °C. To 1.98 mL of 0.5 M zinc chloride, add a 0.5 M solution in THF (0.99 mmol) and stir from -78 °C to room temperature over 15 minutes. 152 mg of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.33 mmol) and 27 mg of PdCl₂ (dppf) (0.033 mmol) are added, the vial is covered with a Teflon cap and heated at 80 °C for 2 days. The reaction is cooled to room temperature, quenched with saturated NH₄Cl and extracted with CH₂Cl₂. The separated CH₂Cl₂ layer is dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel chromatography column (hexane: AcOEt: 2M NH₃ in MeOH = 10: 2: 1) to give 88 mg of the title product. Yield 54%; Mass spectrum (m/e): 461 (M + 1)⁺ ¹H-NMR (CDCl₃), δ 7.98 (s, 1H), 6.77 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 2.55 (s, 3H), 1.88 (m, 4H), 0.92 (t, J = 7.5 Hz, 6H).

Example 49

3-(4-Chloro-2-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation of 1,2-b] pyridazine

175 mg of 3-(4-bromo-2-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.38 mmol) and 56 mg copper chloride (0.57 mmol) were placed in a 4 mL vial with 3.0 mL DMF. Cover with Teflon cap. The vial is heated at 130 °C overnight. The reaction solution is applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1 and hexane: AcOEt = 8: 1) to obtain 91 mg of a crude product. The pure product is recrystallized from 73 mg (46%) Et₂O / Hexane. Mass spectrum (m/e): 415 (M + 1)⁺ ¹H-NMR (CDCl₃), δ 7.98 (s, 1H), 6.80 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 1.88 (m, 4H), 0.92 (t, J = 7.5 Hz, 6H).

Example 50

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-oxazol-5-yl)-imidazo [1,2-b] pyridazine

686 mg 8-(1-ethyl-propyl)-3-oxo-2,6-dimethyl-imidazo [1,2-b] pyridazine (2.0 mmol), 839 mg 4-methyl-oxazole (10 mmol), 105 mg triphenylphosphine (0.4 mmol) and 1.30 g cesium carboxylate (4.0 mmol) are placed in a tube with 10 ml dry DMF. N₂ gas is bubbled for 20 minutes and 92 mg of Pd₂dba₃ (0.1 mmol) is added. The tube is sealed overnight and heated at 130 ° C. After cooling to room temperature, water and CHCl₃ are added to the mixture. The CHCl₃ layer is separated, washed with saturated NaCl, dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel chromatography column (hexane:AcOEt = 5:1) to give 234 mg of the title product. Yield 39%. Mass spectrum (m / e): 299 (M + 1)⁺ ¹H-NMR (CDCl₃): 8.05 (s, 1H), 6.75 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.50 (s, 3H), 2.29 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 51

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-oxazol-2-yl]-Dimethylamine

A. 3-(5-bromo-4-methyl-oxazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine 230 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-oxazol-5-yl)-imidazo [1,2-b] pyridazine (0.77 mmol) is dissolved in 20 ml CH₂Cl₂. 178 mg of NBS (1.0 mmol) is added. The reaction mixture is stirred overnight at room temperature. The reaction mixture is washed with saturated Na₂S₂O₃, saturated NaCl, dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel chromatography column (hexane:AcOEt = 3:1) to give 36 mg of the title compound. Yield 12%. Mass spectrum (m / e): 378 (M + 1)⁺ ¹H-NMR (CDCl₃): 6.82 (s, 1H), 3.39 (m, 1H), 2.58 (s, 3H), 2.53 (s, 3H), 2.26 (s, 3H), 1.85 (m, 1H), 0.89 (t, J = 7.4 Hz, 6H).

B. N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-oxazol-2-yl]-Dimethylamine 32 mg of 3-(5-bromo-4-methyl-oxazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.08 mmol) and 78 mg cesium carboxylate (0.24 mmol) are placed in a vial with 3 ml dimethylamine 2.0M in THF. The vial is covered with a Teflon cap and heated at 110 ° C. for 3 days. The reaction mixture is cooled to room temperature, concentrated and applied onto a silica gel chromatography column (hexane:AcOEt:2M NH₃ in MeOH = 10:2:1) to give 24 mg of the title product. Yield 89%. Mass spectrum (m / e): 342 (M + 1)⁺ ¹H-NMR (CDCl₃): 6.71 (s, 1H), 3.34 (m, 1H), 3.13 (s, 6H), 2.56 (s, 3H), 2.49 (s, 3H), 2.14 (s, 3H), 1.84 (m, 4H), 0.89 (t, J = 7.5 Hz, 6H).

Example 52

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[(4-methyl-2-ethylamino)-thiazol-5-yl]-imidazo [1,2-b] pyridazine

The title compound was prepared in Example 51B using 2.0 ml of ethylamine 2.0M in THF and 152 g of cesium carboxylate (0.56 mmol) (78%). Prepare as described basically in. Mass spectrum (m / e): 358 (M + 1)⁺ ¹H-NMR (CDCl₃): 6.69 (s, 1H), 5.23 (br, 1H), 3.38 (m, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.85 (m, 4H), 1.35 (t, 3H, J = 7.2 Hz), 0.90 (t, 6H, J = 7.2 Hz).

Example 53

3-[5-(2,4-Dimethyl-thiazol-5-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

A mixture of 2,4-dimethylthiazol (0.25 g, 2.04 mmol) and THF (5 mL) at -78 ° C. was charged with 1.6 M t-Bu-Li in hexane (1.30 mL, 2.09 mmol). Added. The mixture is stirred at -78 ° C for 15 minutes. Add 0.5M ZnCl₂ in THF (4.3 mL, 2.14 mmol) and warm the solution to ambient temperature. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol) and PdCl₂(dppf) (0.037 g, 0.051 mmol) were added and the mixture was stirred overnight at 65 ° C., diluted with EtOAc (20 mL), 10% citric acid (15 mL), water (15 mL), Washed with brine (15 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by silica gel chromatography (0-15% EtOAc / hexane gradient) to yield the title compound (0.21 g, 0.49 mmol, 49%). ¹H NMR (CDCl₃): 6.0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.14 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 2.57 (s, 3H), 2.66 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.00 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 425.3; ANALYSIS: 425.2.

ANALYSIS: 425.2.

Example 54

3-[5-(4,5-Dimethyl-thiazol-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 25, from 4,5-dimethylthiazol (0.22 mL, 2.04 mmol) to 1.56 M n-Bu-Li (1.34 mL, 2.09 mmol), ZnCl₂ (4.3 mL, 2.14 mmol), 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] The title compound (0.27 g, 0.54 mmol, 63%) is produced from pyridazine (0.40 g, 1.02 mmol) and PdCl₂(dppf) (0.037 g, 0.051 mmol). ¹H NMR (CDCl₃): 6.0.89 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.13 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.32 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 425.3; ANALYSIS: 425.2.

Example 55

8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-pyridin-4-yl)-thiophen-2-yl]-imidazo [1,2-b] pyridazine

Using a procedure similar to Example 31, 4-bromo-2-methylpyridine (Fukaya et. El. Chem. Pharm. Bull., 1990, 38, 2446) (0.21 g, 1.22 mmol), 1.56 M n-Bu-Li (0.69 mL, 1.07 mmol), THF (2 mL, 1.12 mmol), 0.5M ZnCl₂ in 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol) and PdCl₂(dppf) (0.037 g, 0.051 mmol) To yield the title compound (0.058 g, 0.14 mmol, 14%). ¹H NMR (CDCl₃): 6.0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.16 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 2.58 (s, 3H), 3.27-3.37 (m, 1H), 6.68 (s, 1H), 7.29 (d, J = 5.3 Hz, 1H), 7.35 (s, 1H), 7.41 (s, 1H), 8.46 (t, J = 5.3 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 405.3; ANALYSIS: 405.2.

Example 56

8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-1H-pyrazol-4-yl)-thiophen-2-yl]-imidazo [1,2-b] pyridazine

Using a procedure analogous to Example 31, 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol), 1.42 M n-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M ZnCl₂ in THF (2.14 mL, 1.07 mmol), From 4-bromo-1-methyl-1H-pyrazole (0.25 g, 1.53 mmol) and PdCl₂(dppf) (0.037 g, 0.051 mmol), the title compound (0.092 g, 0.23 mmol, 23%). ¹H NMR (CDCl₃): 6.0.88 (t, J = 7.4 Hz, 6H), 1.73-1.92 (m, 4H), 2.12 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 3.92 (s, 3H), 6.65 (s, 1H), 6.98 (s, 1H), 7.54 (s, 1H), 7.68 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 394.3; ANALYSIS: 394.2.

Example 57

4-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiophen-2-yl]-tetrahydro-Preparation of pyran-4-ol

3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.60 g, 1.53 mmol) and THF (10 mL) at -78 ° C. is added 1.56 M n-Bu-Li (1.93 mL, 1.61 mmol). After 30 minutes, tetrahydro-pyran-4-one (0.21 mL, 2.29 mmol) is added over 5 minutes. The solution is stirred at -78 ° C. for 2 h, warmed to ambient temperature, diluted with EtOAc (50 mL), washed with saturated NH₄Cl (50 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (20% to 100% EtOAc / hexane gradient) to yield the title compound (0.38 g, 0.92 mmol, 60%). ¹H NMR (CDCl₃): 6.0.88 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 1.91-2.00 (m, 2H), 2.11 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.51 (s, 3H), 3.30-3.39 (m, 1H), 3.83-3.93 (m, 5H), 6.65 (s, 1H), 6.93 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 414.3; ANALYSIS: 414.2.

Example 58

8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(tetrahydro-pyran-4-yl)-thiophen-2-yl]-imidazo [1,2-b] Preparation of pyridazine

Method A

4-(5-[8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol (0.25 g, 0.604 mmol) and CH_2I_2 (10 mL), TFA (0.79 mL, 10.28 mmol) and LiAlH_4 (0.25 mL, 1.57 mmol) is added. The solution is concentrated, dissolved in EtOAc (30 mL), washed with saturated NaHCO_3 (30 mL), dried over MgSO_4 , filtered and concentrated. The residue was purified by ISCO column chromatography (10% to 15% EtOAc / hexane gradient), dissolved in EtOH (25 mL), 10% Pd / C (0.07 g, 0.066 mmol) was added and the solution is stirred under H_2 medium. After 2 hours, the solution is filtered through Celite® and concentrated. The residue is purified by ISCO column chromatography (30% EtOAc in hexanes) to yield the title compound (0.033 g, 0.083 mmol, 14%). $^1\text{H NMR}$ (CDCl_3), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.95 (m, 4H), 1.97-2.04 (m, 2H), 2.09 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.52 (s, 3H), 3.00-3.11 (m, 1H), 3.30-3.40 (m, 1H), 3.54 (dt, J = 11.8, 2.2 Hz, 2H), 4.56 (dd, J = 11.9, 2.2 Hz, 2H), 6.65 (s, 1H), 6.75 (s, 1H). LC / MS (m / z) : calcd $[\text{M} + \text{H}]^+$ 398.2; ANALYSIS: 398.2.

Method B

A, 4-(5-Bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol (2.0 g, 17.75 mmol) and THF (30 mL) To a -78 ° C. solution of 2.0M LDA (9.32 mL, 18.63 mmol) is added. After 30 minutes, tetrahydro-pyran-4-one (2.3 mL, 23.07 mmol) is added at -78 ° C. and the solution is warmed to ambient temperature. The solution is washed with saturated NH_4Cl (30 mL). The aqueous phase is extracted with EtOAc. The combined organic layers are dried over MgSO_4 and concentrated.

The residue is purified by ISCO column chromatography (30% to 100% EtOAc / hexane gradient) to yield the title compound (2.3 g, 8.30 mmol, 47%). $^1\text{H NMR}$ (CDCl_3), δ 1.82 (m, 2H), 2.00 (s, 3H), 2.06-2.15 (m, 3H), 2.16 (s, 3H), 3.77-3.84 (m, 2H), 3.87 (dt, J = 11.3, 2.2 Hz, 2H), 6.67 (s, 1H). LC / MS (m / z) : calcd $[\text{M} + \text{H}]^+$ 277.0; ANALYSIS: 260.9.

8-(4-(5-Bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-yl)-5-bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol (2.3 g, 8.30 mmol) and 1,2-dichloroethane (50 mL) are added. ZnCl_2 (3.97 g, 12.45 mmol) and sodium cyanoborohydride (3.91, 62.23 mmol). The solution is stirred for 1 hour, filtered through celite and concentrated. The

residue is purified by ISCO column chromatography (5-10% EtOAc / hexane gradient) to yield the title compound (1.53 g, 5.86 mmol, 71%). $^1\text{H NMR}$ (CDCl_3), δ 1.69-1.82 (m, 2H), 1.84-1.92 (m, 2H), 2.14 (s, 3H), 2.84-2.98 (m, 1H), 3.49 (dt, J = 11.8, 2.2 Hz, 2H), 4.00-4.07 (m, 2H), 6.51 (s, 1H).

C, 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(tetrahydro-pyran-4-yl)-thiophen-2-yl]-imidazo [1,2-b] Pyridazine Using a procedure similar to that of Example 25, 4-(5-bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran (0.83 g, 3.19 mmol), 1.56 M n-BuLi (2.04 mL, 3.19 mmol), ZnCl_2 (6.4 mL, 3.19 mmol), 8-(1-ethyl-propyl)-3-yl-2,6-dimethyl-[1,2-b] pyridazine (0.50 g, 1.56 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.068 mmol) of the title compound from (0.072g, 0.18 mmol, 11%) to produce A. Same spectrum as Method A.

Example 59

3-[5-(3,4-Difluoro-phenyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] Preparation of pyridazine

Using a procedure similar to that in Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.50 g, 1.27 mmol) and PdCl_2 (dppf) (0.047g, 0.064 mmol) and THF (5.1 mL, 2.55 mmol) in 3,4-difluoro-phenyl zinc bromide. The 0.5 M solution is reacted. The residue was purified by ISCO column chromatography (15-20% EtOAc / hexane gradient) and chromatographed (50 x 250 C18 control column, 30-80% water: 0.1% TFA / ACN: 0.1% TFA gradient) to yield the title compound (0.18 g, 0.42 mmol, 33%). $^1\text{H NMR}$ (CDCl_3), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.13-7.21 (m, 1H), 7.18 (s, 1H), 7.31-7.36 (m, 1H), 7.39-7.46 (m, 1H). LC / MS (m / z) : calcd $[\text{M} + \text{H}]^+$ 426.3; ANALYSIS: 426.2.

Example 60

Preparation of 3-(5-benzyl-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.765 mmol) and PdCl_2 (dppf) (0.028g, 0.038 mmol) and THF (4.6 mL, 2.29 mmol) and a solution of 0.5M benzyl zinc bromide. The residue was purified by ISCO column chromatography (15% -20% EtOAc / hexane gradient) and chromatographed (50 x 250 C18 Symmetry column, 40-65% water: 0.1% TFA / ACN: 0.1% TFA gradient) to yield the title compound (0.062 g, 0.15 mmol, 20%). $^1\text{H NMR}$ (CDCl_3), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.51 (s, 3H), 3.29-3.39 (m, 1H), 4.16 (s, 2H), 6.65 (s, 1H), 6.68 (s, 1H), 7.22-7.29 (m, 1H), 7.31-7.36 (m, 4H). LC / MS (m / z) : calcd $[\text{M} + \text{H}]^+$ 404.3; ANALYSIS: 404.2.

Example 61

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-4-pyridin-3-yl-thiophen-2-yl]-imidazo [1,2-b] pyridazine

3-(4-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25 g, 64 mmol), pyridine-3-boronic acid (0.086 g, 0.70 mmol), 2M Na_2CO_3 (0.48 mL, 0.96 mmol) and n-PrOH (3 mL) was degassed with nitrogen for 10 min. To do. Pd(OAc) $_2$ (2.7 mg, 0.0013 mmol) and PPh_3 (0.010 g, 0.038 mmol) are added and the solution is heated at 90 ° C. overnight. The solution is diluted with EtOAc (30 mL), washed with 10% Na_2CO_3 (30 mL) water (30 mL), brine (30 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO (20-40% EtOAc gradient) to yield the title compound (0.051 g, 0.13 mmol, 20%). $^1\text{H NMR}$ (CDCl_3), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.09 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.29-3.40 (m, 1H), 6.69 (s, 1H), 7.33-7.43 (m, 1H), 7.47 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 8.61 (bs, 1H), 8.78 (bs, 1H). LC / MS (m / z) : calcd $[\text{M} + \text{H}]^+$ 391.2; ANALYSIS: 391.4.

Example 62

8-(1-Ethyl-propyl)-3-[5-(6-methoxy-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo [1,2-b] Preparation of pyridazine

Using a procedure similar to that in Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.765 mmol) and PdCl_2 (dppf) (0.028g, 0.038 mmol) and THF (3.6 mL, 1.53 mmol) solution of 6-methoxy-2-pyridyl zinc bromide. The title compound (0.12 g, 0.29 mmol, 38%) is produced from a 0.5 M solution of $^1\text{H NMR}$ (CDCl_3), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 3.98 (s, 3H), 6.61 (d, J = 7.5 Hz, 1H), 6.70 (s, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H). LC / MS (m / z) : calcd $[\text{M} + \text{H}]^+$ 421.3; ANALYSIS: 421.3.

Example 63

8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(4-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo [1,2-b] Production method of pyridazine.

Using a procedure similar to that in Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.765 mmol) and PdCl_2 (dppf) (0.028g, 0.038 mmol) and THF (3.6 mL, 1.53 mmol) in 4-methyl-2-pyridyl zinc bromide. The title compound (0.21 g, 0.52 mmol, 68%) is produced from a 0.5 M solution of

¹ H NMR (CDCl₃), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.45 (s, 3H), 2.52 (s, 6H), 3.30-3.40 (m, 1H), 6.67 (s, 1H), 6.97 (d, J = 4.8 Hz, 1H), 7.49 (s, 1H), 7.52 (s, 1H), 8.42 (d, J = 4.8 Hz, 1H). LC / MS (m/z): calcd M + H⁺: 405.3; ANALYSIS: 405.3.

Example 64

8- (1-Ethyl-propyl) -2,6-dimethyl-3- [3-methyl-5- (3-methyl-pyridin-2-yl) -thiophen-2-yl] -imidazo [1,2-b] Preparation of pyridazine

Using a procedure similar to that of Example 32, 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethylimidazo [1,2-b] pyridazine (0.30 g, 0.765 mmol), 3-methyl-2-pyridylzinc in PdCl₂ (dppf) (0.028 g, 0.038 mmol) and THF (5.0 mL, 2.50 mmol) The title compound (0.22 g, 0.54 mmol, 71%) is produced from a 0.5 M solution of bromide ¹ H NMR (CDCl₃), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 2.63 (s, 3H), 3.29-3.39 (m, 1H), 6.67 (s, 1H), 7.06-7.14 (m, 1H), 7.44 (s, 1H), 7.74 (dd, J = 7.5, 0.9 Hz, 1H), 8.47 (dd, J = 4.9, 0.9 Hz, 1H) LC / MS (m/z). Calculated value C₂₄H₂₈N₄S (M + H)⁺: 405.3; ANALYSIS: 405.3

Example 65

(6- (5- [8- (1-Ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl] -4-methyl-thiophen-2-yl) -pyridine Preparation of 2-yl) -dimethyl-amine

Using a procedure similar to Example 39, Rieke® Zn, (5-bromo-pyridin-2-yl) -dimethyl-amine (Newkome et al.) in THF (0.20 g, 3.06 mmol). J. Org. Chem., 1988, 3, 786) (0.41 mL, 2.04 mmol), 3- (5-bromo-3-methyl-thiophen-2-yl) -6- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.35 g, 0.89 mmol) and PdCl₂ (dppf) (0.037 g, 0.051 mmol) to give the title compound (0.16 g, 0.37 mmol, 36%). ¹ H NMR (CDCl₃), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.21 (s, 6H), 3.30-3.40 (m, 1H), 6.40 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 6.95 (d, J = 7.4 Hz, 1H), 7.45 (dd, J = 8.4, 7.4 Hz, 1H), 7.46 (s, 1H). LC / MS (m/z): calcd M + H⁺: 434.3; ANALYSIS: 434.3.

Example 66

8- (1-Ethyl-propyl) -2,6-dimethyl-3- [3-methyl-5- (5-methyl-pyridin-2-yl) -thiophen-2-yl] -imidazo [1,2-b] Preparation of pyridazine

Using a procedure similar to that in Example 32, 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.765 mmol) and PdCl₂ (dppf) (0.028 g, 0.038 mmol) and THF (3.0 mL, 1.53 mmol) in 4-methyl-2-pyridyl zinc bromide The title compound (0.23 g, 0.57 mmol, 74%) is produced from a 0.5 M solution of ¹ H NMR (CDCl₃), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.16 (s, 3H), 2.35 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.48 (s, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 8.39-8.40 (m, 1H). LC / MS (m/z): calcd M + H⁺: 405.3; ANALYSIS: 405.3.

Example 67

8- (1-Ethyl-propyl) -3- [5- (6-methanesulfonyl-pyridin-2-yl) -3-methyl-thiophen-2-yl] -2,6-dimethyl-imidazo [1,2-b] Preparation of pyridazine

A, 2-bromo-6-methanesulfonyl-pyridine 2-bromo-6-methylsulfonyl-pyridine (Testaferri et al. Tetrahedron, 1985, 41, 1979) (2.15 g, 10.53 mmol) and C₆H₅Cl (30 mL) To the solution is added 56-87% mCPBA (12 g, 42.15 mmol). The solution was cooled to room temperature with ice, the solution was stirred for 2 h, washed with saturated Na₂S₂O₃ (15 mL), saturated NaHCO₃ (2 x 15 mL), dried over MgSO₄, filtered. Concentrate. The residue is purified by recrystallization from EtOAc / hexanes to yield the title compound (1.71 g, 7.24 mmol, 69%). ¹ H NMR (CDCl₃), δ 3.26 (s, 3H), 7.73 (dd, J = 8.0, 0.9 Hz, 1H), 7.82 (dd, J = 8.0, 7.5 Hz, 1H), 8.05 (dd, J = 7.5, 0.9 Hz, 1H). LC / MS (m/z): Calcd M + H⁺: 235.9; ANALYSIS: 235.9.

8- (1-Ethyl-propyl) -3- [5- (6-methanesulfonyl-pyridin-2-yl) -3-methyl-thiophen-2-yl] -2,6-dimethyl-imidazo [1,2-b] pyridazine Using a procedure similar to that in Example 25, 2-bromo-6-methanesulfonyl-pyridine (0.29 mL, 1.22 mmol), 1.3 M n-Bu-Li (0.82 mL, 1.22 mmol), ZnCl₂ (2.14 mL, 1.07 mmol), 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol) and PdCl₂ (dppf) (0.037 g, 0.051 mmol), afforded the titled compound (0.13 g, 0.28 mmol 27%) is generated. ¹ H NMR (CDCl₃), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30 (s, 3H), 3.30-3.38 (m, 1H), 6.70 (s, 1H), 7.64 (s, 1H), 7.83 (dd, J = 7.6, 0.8 Hz, 1H), 7.89 (dd, J = 7.9, 0.8 Hz, 1H), 7.93 (dd, J = 7.9, 7.6 Hz, 1H). LC / MS (m/z): calcd S 2 (M + H)⁺: 469.3; ANALYSIS: 469.2.

Example 68

8- (1-Ethyl-propyl) -2,6-dimethyl-3- [3-methyl-5- (6-trifluoromethyl-pyridin-2-yl) -thiophen-2-yl] -imidazo [1,2-b] Preparation of pyridazine

Using a procedure similar to Example 25, 2-chloro-6-trifluoromethyl-pyridine (0.29 mL, 1.22 mmol), 1.34 M n-Bu-Li (0.80 mL, 1.07 mmol), ZnCl₂ (2.14 mL, 1.07 mmol), 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol) and PdCl₂ (dppf) (0.037 g, 0.051 mmol) produce the title compound (0.20 g, 0.44 mmol, 43%). ¹ H NMR (CDCl₃), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.30-3.40 (m, 1H), 6.59 (s, 1H), 7.50 (dd, J = 7.5, 0.9 Hz, 1H), 7.65 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.84 (dd, J = 7.9, 7.5 Hz, 1H). LC / MS (m/z): calcd S (M + H)⁺: 459.3; ANALYSIS: 459.2.

Example 69

8- (1-Ethyl-propyl) -2,6-dimethyl-3- [3-methyl-4- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiophene-2-yl] -imidazo [1,2-b] pyridazine

To a slurry of 0.05 g / mL Rieke® Zn in THF (3.0 mL, 2.29 mmol) was added triazol of 5-bromo-1-methyl-1H- [1,2,4] and Add a solution of THF (2 mL). The solution is heated at 65 ° C. for 1 hour, cooled to room temperature, and excess Zn is fixed for 1 hour. The solution was dissolved in 3- (4-bromo-3-methyl-thiophen-2-yl) -6- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (Example Wrap). -152) transfer (0.32 g, 0.70 mmol) and PdCl₂ (dppf) (0.028 g, 0.038 mmol) to a flask containing. The solution is heated at 65 ° C. overnight, diluted with EtOAc (30 mL), washed with saturated NH₄Cl (30 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO (50%-100% Et₂O) to yield the title compound (0.058 g, 0.15 mmol, 19%). ¹ H NMR (CDCl₃), δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.11 (s, 3H), 2.47 (s, 3H), 2.49 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.68 (s, 1H), 7.64 (s, 1H), 7.9 (s, 1H). LC / MS (m/z): calcd M + H⁺: 395.2; ANALYSIS: 395.4.

Example 70

1- (6- (5- [8- (1-Ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl] -4-methyl-thiophen-2-yl) -pyridin-2-yl) -ethanone preparation

A, 3- [5- (6-bromo-pyridin-2-yl) -3-methyl-thiophen-2-yl] -8- (1-ethyl-propyl) -2,6-dimethylimidazo [1,2-b] Pyridazine Using a procedure similar to Example 25, 2,6-dibromo-pyridine (0.91 g, 3.82 mmol), 1.34 M n-Bu-Li (1.50 mL, 2.00 mmol), ZnCl₂ (4.0 mL, 2.00 mmol), 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.75 g, 1.92 mmol) from and PdCl₂ (dppf) (0.070 g, 0.096 mmol), and generates the title compound (0.26 g, 0.55 mmol, 29%). ¹ H NMR (CDCl₃), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.31 (dd, J = 7.5, 1.3 Hz, 1H), 7.49-7.57 (m, 2H), 7.58 (s, 1H).

B, 1- (6- (5- [8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl] -4-methyl-thiophen-2-yl) -pyridin-2-yl) -ethanone 3- [5- (6-bromo-pyridin-2-yl) -3-methyl-thiophen-2-yl] -8- (1-ethyl-propyl) -2,6-dimethylimidazo [1,2-b] pyridazine (0.26 g, 0.55 mmol) and THF (5 mL) in a -78 ° C solution to 1.34 M n-Bu-Li (0.43 mL, 0.58 mmol) is added. After 30 minutes, N-methoxy-N-methyl-acetamide (0.065 mL, 0.61 mmol) is added and the solution is warmed to ambient temperature. The solution is diluted with

EtOAc (30 mL), washed with saturated NH_4Cl (25 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (15-20% EtOAc / hexane gradient) to yield the title compound (0.030 g, 0.069 mmol, 13%). $^1\text{H NMR}$ (CDCl_3) δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.19 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 2.77 (s, 3H), 3.30-3.40 (m, 1H), 6.59 (s, 1H), 7.59 (s, 1H), 7.77-7.85 (m, 2H), 7.87 (dd, J = 6.8, 2.2 Hz, 1H). LC / MS (m / z): calcd $\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}_5$ (M + H) $^+$: 433.3; ANALYSIS: 433.2.

Example 71

8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(5-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl)-imidazo [1,2-b] Preparation of pyridazine
Using a procedure similar to Example 32, 2-bromo-5-trifluoromethyl-pyridine (2.14 mL, 1.07 mmol), 1.34 M n-Bu-Li (0.80 mL, 1.07 mmol), ZnCl_2 (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 0.02 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.037 g, 0.051 mmol) produce the title compound (0.17 g, 0.37 mmol, 36%). $^1\text{H NMR}$ (CDCl_3) δ 0.90 (t, J = 7.3 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.19 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 5.70 (s, 1H), 7.63 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 8.4, 2.2 Hz, 1H), 7.79-7.82 (m, 1H). LC / MS (m / z): calcd $\text{C}_{28}\text{H}_{32}\text{N}_4\text{F}_3$ (M + H) $^+$: 459.3; ANALYSIS: 459.2.

Example 72

Preparation of 8-(1-ethyl-propyl)-3-(5-methoxymethyl-3-methyl-thiophen-2-yl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.76 mmol) and THF (3 mL) at -78 ° C. is added 1.34 M n-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes, iodo-methoxy-methane (0.097 mL, 1.15 mmol) is added and the solution is warmed to ambient temperature. After 1 hour, the solution is diluted with EtOAc (40 mL), washed with water (30 mL), brine (30 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (15% to 20% EtOAc / hexane gradient) to yield the title compound (0.12 g, 0.34 mmol, 44%). $^1\text{H NMR}$ (CDCl_3) δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.09 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.28-3.37 (m, 1H), 3.44 (s, 3H), 4.61 (s, 2H), 5.65 (s, 1H), 6.93 (s, 1H). LC / MS (m / z): calcd $\text{C}_{28}\text{H}_{32}\text{N}_4\text{O}_5$ (M + H) $^+$: 358.3; ANALYSIS: 358.3.

Example 73

Of 3-(5-(2-Ethoxy-ethyl)-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation
Using a procedure similar to that in Example 72, 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.76 mmol), 1.34 M n-Bu-Li (0.53 mL, 0.84 mmol), 1-bromo-2-ethoxy-ethane (0.13 mL, 1.15 mmol) and KI (0.013 g, 0.076 mmol) yields the title compound (0.11 g, 0.29 mmol, 38%). $^1\text{H NMR}$ (CDCl_3) δ 0.86 (t, J = 7.5 Hz, 6H), 1.23 (t, J = 7.0 Hz, 3H), 1.72-1.90 (m, 4H), 2.05 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.09 (t, J = 7.0 Hz, 2H), 3.28-3.37 (m, 1H), 3.55 (q, J = 7.0 Hz, 2H), 3.71 (t, J = 7.0 Hz, 2H), 6.64 (s, 1H), 6.77 (s, 1H). LC / MS (m / z): Calculated value $\text{C}_{22}\text{H}_{31}\text{N}_3\text{O}_5$ (M + H) $^+$: 386.3 Analytical value: 386.3.

Example 74

(5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiophen-2-yl)-phenyl-methano- Preparation
A. (5-bromo-4-methyl-thiophen-2-yl)-phenyl-methanol is 2-bromo-3-methyl-78 ° C. thiophene (4.7g, 26.54mmol) and Et_2O (100 mL) is added to 2.0 M LDA (14.6 mL, 29.2 mmol). After 1 hour, benzaldehyde (3.0 mL, 29.2 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hours. The solution is washed with saturated NH_4Cl (75 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (20% to 30% EtOAc / hexane gradient) to yield the title compound (3.29 g, 11.62 mmol, 44%). $^1\text{H NMR}$ (CDCl_3) δ 2.11 (s, 3H), 3.36-3.46 (m, 1H), 5.90 (s, 1H), 6.54 (s, 1H), 7.30-7.45 (m, 5H). LC / MS (m / z): calcd $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_2$ (M + H) $^+$: 281.9, 283.0; analysis: 264.9, 266.9.

B. (5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiophen-2-yl)-phenyl-methano- Using a procedure similar to that of the 300 example, 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.15 mmol), (5-bromo-4-methyl-thiophen-2-yl)-phenyl-methanol (0.33 g, 1.15 mmol), 2M Na_2CO_3 (0.80 mL, 1.72 mmol) n-PrOH (1 mL), $\text{Pd}(\text{OAc})_2$ (0.0052g, 0.023mmol) residues from and pph₃ (0.018, 0.069mmol) ! Purified by SCO column chromatography (20% -30% EtOAc / hexane gradient) and chromatographed (50 x 250 C18 Symmetry column, 25-75% water: 0.1% TFA / ACN: 0.1% To give the title compound (0.017 g, 0.041 mmol, 3.5%). $^1\text{H NMR}$ (CDCl_3) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.04 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 2.75 (bs, 1H), 3.26-3.38 (m, 1H), 6.05 (s, 1H), 6.65 (s, 1H), 6.76 (s, 1H), 7.30-7.45 (m, 3H), 7.50-7.56 (m, 1H). LC / MS (m / z): calcd $\text{C}_{30}\text{H}_{33}\text{N}_3\text{O}_5$ (M + H) $^+$: 420.3; ANALYSIS: 420.3.

Example 75

Preparation of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (4.00 g, 10.0 mmol) and AcOH (40 mL), Br_2 (0.57 mL, 11.21 mmol) is added and the solution is heated at 110 ° C. overnight. Br_2 (0.57 mL, 11.21 mmol) is added and the solution is heated at 110 ° C. for 2 hours. The solution is poured into 5M NaOH (200 mL) and ice (200 mL). The slurry is extracted with EtOAc (2 x 150 mL). The combined organic layers are washed with water (200 mL), 20% NaHSO_3 (200 mL), saturated NaHCO_3 (200 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO (5% to 15% EtOAc gradient) to yield the title compound (2.66 g, 5.64 mmol, 55%). $^1\text{H NMR}$ (CDCl_3) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.12 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 3.25-3.35 (m, 1H), 6.69 (s, 1H). LC / MS (m / z): calcd $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_2$ (M + H) $^+$: 470.0; ANALYSIS: 470.3.

Example 76

Preparation of 3-(4-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
3-(4,5-Dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.22 g, To a -78 ° C. solution of 0.47 mmol) and THF (3 mL) is added 1.6 M n-BuLi (0.31 mL, 0.49 mmol). After 20 minutes, the solution is quenched with water (1 mL), warmed to ambient temperature, diluted with EtOAc (30 mL), washed with brine (30 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO (5% to 10% EtOAc gradient) to yield the title compound (0.055 g, 0.14 mmol, 31%). $^1\text{H NMR}$ (CDCl_3) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.68 (s, 1H), 7.44 (s, 1H). LC / MS (m / z): calcd $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_2$ (M + H) $^+$: 392.2; ANALYSIS: 392.3.

Example 77

3-(2,6-Dimethyl-3-(3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl)-imidazo [1,2-b] pyridazin-8-yl) Preparation of pentane-3-ol
A. 2-(5-bromo-4-methyl-thiophen-2-yl)-5-methyl-pyridine 2-bromo-3-methyl-thiophene (2.0 mL, 17.75 mmol) and THF (30 mL) at -78 ° C. is added to 2.0 M LDA (9.76 mL, 19.52 mmol). After 45 minutes, 0.5M ZnCl_2 (39.0 mL, 19.50 mmol) is added and the solution is stirred for 30 minutes. 2-Bromo-6-methyl-pyridine (2.4 mL, 21.29 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.50 g, 0.44 mmol) are added and the solution is warmed to ambient temperature and stirred for 2 hours. The solution is washed with saturated NH_4Cl

(20 mL). Extract the aqueous layer with CH_2Cl_2 (30 mL). The combined organic layer is washed with saturated NH_4Cl (20 mL), dried over Na_2SO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (10% to 20% EtOAc / hexane gradient) to yield the title compound (2.34 g, 8.73 mmol, 49%). ^1H NMR (CDCl_3), δ 2.21 (s, 3H), 2.54 (s, 3H), 6.99 (d, J = 7.9 Hz, 1H), 7.23 (s, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.53 (dd, J = 7.9, 7.9 Hz, 1H). LC / MS (m / z): Calculated value $\text{C}_{11}\text{H}_{10}\text{BrN}_4\text{S}$ (M + H)⁺: 267.0, 269.0; Analytical values: 267.7, 269.5.

B. 2,6-Dimethyl-3-[(3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl)-imidazo[1,2-b]pyridazin-2-yl]-pyridazine (below) (0.50 g, 3.39 mmol), 2-(5-bromo-4-methylthiophen-2-yl)-6-methyl-pyridine (1.00 g, 3.73 mmol), Cs_2CO_3 (2.32 g, 7.13 mmol) and DMF (5 mL) are degassed with N_2 for 15 min. $\text{Pd}_2(\text{dba})_3$ (0.15 g, 0.16 mmol) and PPh_3 (0.17 g, 0.65 mmol) are added and the solution is heated at 130 °C overnight. The solution is diluted with CH_2Cl_2 (30 mL), washed with water (2 x 25 mL), brine (25 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (100% EtOAc) and then recrystallized from acetonitrile / water to yield the title compound (0.45 g, 1.35 mmol, 39%). ^1H NMR (CDCl_3), δ 2.13 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 2.57 (s, 3H), 6.90 (d, J = 9.2 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 8.0, 7.5 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H). LC / MS (m / z): calcd (C₂₂H₂₂N₄S) (M + H)⁺: 335.1; ANALYSIS: 335.1.

C. 1-[(2,6-dimethyl-3-[(3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl)-imidazo[1,2-b]pyridazin-8-yl]-Propan-1-one 2,6-dimethyl-3-[(3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl)-imidazo[1,2-b]pyridazine To a -78 °C solution of (0.34 g, 1.02 mmol) and THF (9 mL) is added 2.0 M LDA (0.61 mL, 1.22 mmol). After 3 minutes, N-methoxy-N-methyl-propionamide (Wolberg et. El. Chem. Eur. J., 2001, 7, 4562) (1.17 g, 1.42 mmol) was added and the solution was stirred for 20 minutes. And warm to room temperature and stir for 30 minutes. The solution is diluted with EtOAc (50 mL), washed with saturated NH_4Cl (30 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (20% to 30% EtOAc / hexane gradient) to yield the title compound (0.10 g, 0.26 mmol, 25%). ^1H NMR (CDCl_3), δ 1.28 (t, J = 7.0 Hz, 3H), 2.13 (s, 3H), 2.54 (s, 3H), 2.58 (s, 6H), 3.59 (q, J = 7.0 Hz, 2H), 7.03 (d, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.55 (bs, 1H), 7.58 (dd, J = 7.9, 7.5 Hz, 1H). LC / MS (m / z): calcd (C₂₂H₂₂N₄OS) (M + H)⁺: 391.2; ANALYSIS: 391.2.

D. 3-[(2,6-Dimethyl-3-[(3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl)-imidazo[1,2-b]pyridazin-8-yl]-Pentane-3-ol 1-[(2,6-dimethyl-3-[(3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl)-imidazo[1,2-b]pyridazin-8-yl]-propan-1-one (0.040 g, 0.10 mmol) and Et₂O (5 mL) in a -0 °C solution of 3.0 Methyl magnesium bromide (0.68 mL, 2.05 mmol) is added. The solution is warmed to ambient temperature, diluted with EtOAc (30 mL), washed with saturated NH_4Cl (20 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (20% to 30% EtOAc / hexane gradient) to yield the title compound (0.016 g, 0.036 mmol, 37%). ^1H NMR (CDCl_3), δ 0.89 (t, J = 7.4 Hz, 6H), 1.92-2.01 (m, 4H), 2.14 (s, 3H), 2.46 (s, 3H), 2.53 (s, 3H), 3.57 (s, 3H), 6.99 (s, 1H), 6.66 (s, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.57 (dd, J = 7.9, 7.5 Hz, 1H). LC / MS (m / z): calcd (C₂₆H₂₆N₄OS) (M + H)⁺: 421.3; ANALYSIS: 421.3.

Example 78

Of 8-[(1-ethyl-propyl)-2,6-dimethyl-3-[(3-methyl-4-thiazol-2-yl-thiophen-2-yl)-imidazo[1,2-b]pyridazin-8-yl]-pyridazine Preparation 3-(4-Bromo-3-methylthiophen-2-yl)-8-[(1-ethyl-propyl)-2,6-dimethylimidazo[1,2-b]pyridazin-2-yl]pyridazine (0.25 g (0.5M 2-thiazolyl zinc bromide (3.82 mL, 1.91 mmol) is added to a flask containing 54 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.023 g, 0.032 mmol). Heat at 0 °C, dilute with EtOAc (30 mL), wash with saturated NH_4Cl (25 mL), dry over MgSO_4 , filter and concentrate. The residue is ISCO (15% to 20% EtOAc gradient) was purified by the title compound (0.19 g, 0.48 mmol, 76%) to produce a ^1H NMR (CDCl_3) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.36 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 3.29-3.39 (m, 1H), 6.69 (s, 1H), 7.33 (d, J = 3.3 Hz, 1H), 7.89 (d, J = 3.3 Hz, 1H), 7.99 (s, 1H). LC / MS (m / z): calcd (C₂₂H₂₂N₄S) (M + H)⁺: 397.2; ANALYSIS: 397.3.

Example 79

Preparation of 8-[(1-ethyl-propyl)-2,6-dimethyl-3-[(3-methyl-5-o-tolyl-thiophen-2-yl)-imidazo[1,2-b]pyridazin-2-yl]pyridazine Using a procedure analogous to Example 32, 3-(5-bromo-3-methylthiophen-2-yl)-8-[(1-ethyl-propyl)-2,6-dimethylimidazo[1,2-b]pyridazin-2-yl]pyridazine (0.15 g, 0.38 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.014 g, 0.019 mmol) and THF (3 mL, 1.53 mmol) 0.5M solution of 2-methylphenyl zinc iodides in To yield the title compound (0.069 g, 0.17 mmol, 45%). ^1H NMR (CDCl_3) δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.19 (s, 3H), 2.53 (s, 3H), 2.54 (s, 3H), 2.55 (s, 3H), 3.32-3.40 (m, 1H), 6.68 (s, 1H), 7.02 (s, 1H), 7.22-7.30 (m, 3H), 7.48-7.53 (m, 1H). LC / MS (m / z): calcd (C₂₅H₂₅N₄S) (M + H)⁺: 404.3; ANALYSIS: 404.3.

Example 80

Of (5-[(1-ethyl-propyl)-2,6-dimethylimidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiophen-2-yl)-phenyl-methanone Preparation 3-(5-Bromo-3-methylthiophen-2-yl)-8-[(1-ethyl-propyl)-2,6-dimethylimidazo[1,2-b]pyridazin-2-yl]pyridazine (0.30 g, 76 mmol) and THF (5 mL) at -78 °C is added 1.30 M n-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes, N-methoxy-N-methyl-benzamide (0.13 mL, 0.84 mmol) is added and the solution is warmed to ambient temperature and stirred overnight. The solution is diluted with EtOAc (20 mL), washed with saturated NH_4Cl (15 mL), water (15 mL), brine (15 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (15% to 20% EtOAc / hexane gradient) to yield the title compound (0.066 g, 0.16 mmol, 21%). ^1H NMR (CDCl_3), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.49-7.54 (m, 2H), 7.56 (s, 1H), 7.57-7.62 (m, 1H), 7.89-7.94 (m, 2H). LC / MS (m / z): calcd (C₂₅H₂₇N₄O) (M + H)⁺: 418.2; ANALYSIS: 418.2.

Example 81

Of 8-[(1-ethyl-propyl)-2,6-dimethyl-3-[(3-methyl-5-oxazol-2-yl-thiophen-2-yl)-imidazo[1,2-b]pyridazin-2-yl]pyridazine Preparation To a solution of oxazole (0.14 g, 2.04 mmol) and THF (3 mL) at -78 °C is added 1.6 M t-Bu-Li in hexane (1.32 mL, 2.14 mmol). The mixture is stirred at -78 °C for 15 minutes. 0.5M ZnCl_2 in THF (4.3 mL, 2.14 mmol) is added and the solution is warmed to ambient temperature. 3-(5-Bromo-3-methylthiophen-2-yl)-8-[(1-ethyl-propyl)-2,6-dimethylimidazo[1,2-b]pyridazin-2-yl]pyridazine (0.40 g, 1.02 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.037 g, 0.051 mmol) were added and the mixture was stirred overnight at 65 °C, diluted with EtOAc (30 mL), 10% citric acid (20 mL), water (20 mL), washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated. The residue was purified by ISCO column chromatography (20% EtOAc / hexane gradient) and chromatographed (50 x 250 C18 Symmetry column, 20-70% water: 0.1% TFA / ACN: 0.1% TFA gradient) to yield the title compound (0.020 g, 0.053 mmol, 5%). ^1H NMR (CDCl_3), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.69 (s, 1H), 7.19 (s, 1H), 7.59 (s, 1H), 7.65 (s, 1H). LC / MS (m / z): Calculated value $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_2$ (M + H)⁺: 381.3; Analytical value: 381.1.

Example 82

8-[(1-Ethyl-propyl)-2,6-dimethyl-3-[(3-methyl-5-(5-methyl-furan-2-yl)-thiophen-2-yl)-imidazo[1,2-b]pyridazin-2-yl]pyridazine Preparation To a 0 °C mixture of 2-methylfuran (0.18 mL, 2.04 mmol) and Et₂O (2 mL) is added 1.6 M t-Bu-Li in hexane (1.30 mL, 2.14 mmol). The mixture is heated at reflux for 30 minutes, cooled to 0 °C, 0.5 M ZnCl_2 in THF (4.3 mL, 2.14 mmol) is added and the solution is warmed to ambient temperature. 3-(5-Bromo-3-methylthiophen-2-yl)-8-[(1-ethyl-propyl)-2,6-dimethylimidazo[1,2-b]pyridazin-2-yl]pyridazine (0.40 g, 1.02 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.037 g, 0.051 mmol) were added and the mixture was stirred overnight at 65 °C, diluted with EtOAc (30 mL), 10% citric acid (20 mL), water (20 mL), washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated. The residue was purified by ISCO column chromatography (20% EtOAc / hexane gradient) and chromatographed (50 x 250 C18 Symmetry column, 20-70% water: 0.1% TFA / ACN: 0.1% TFA gradient) to yield the title compound (0.020 g, 0.053 mmol, 5%). ^1H NMR (CDCl_3), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.69 (s, 1H), 7.19 (s, 1H), 7.59 (s, 1H), 7.65 (s, 1H). LC / MS (m / z): Calculated value $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_2$ (M + H)⁺: 381.3; Analytical value: 381.1.

(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.037 g, 0.051 mmol) were added and the mixture was stirred overnight at 65 ° C, diluted with EtOAc (30 mL), 10% citric acid (15 mL), water (15 mL), washed with brine (15 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc / hexane gradient) to yield the title compound (0.29 g, 0.51 mmol, 50%). $^1\text{H NMR}$ (CDCl_3), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.12 (s, 3H), 2.35 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 5.52 (dd, J = 3.1, 0.9 Hz, 1H), 6.40 (d, J = 3.1 Hz, 1H), 6.66 (s, 1H), 7.12 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 394.3; ANALYSIS: 394.2.

Example 83

Preparation of 3- (3-chloro-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine

A flask of 2-bromo-3-chloro-thiophene (Lemaire et. al., Synth. Commun., 1994, 24, 95) (2.55 g, 12.82 mmol) in THF (25 mL, 19.24 mmol). Add 0.05 g / mL. Reike (R) zinc. The solution is heated at reflux for 2 hours. Excess zinc was fixed and the solution was 8- (1-ethyl-propyl) -3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine (Example KW1-A03735-193) (Transfer to a flask containing 2.01 g, 6.41 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.23 g, 0.32 mmol). The solution is heated at reflux overnight, quenched with saturated NH_4Cl (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layer is dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (2-15% EtOAc / hexane gradient) to yield the title compound (1.32 g, 6.68 mmol, 62%). $^1\text{H NMR}$ (CDCl_3), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.48 (s, 3H), 2.49 (s, 3H), 3.37-3.36 (m, 1H), 6.67 (s, 1H), 7.07 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 334.1; ANALYSIS: 334.1.

Example 84

Preparation of 3- (5-bromo-3-chloro-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine

3- (3-Chloro-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine solution (1.15 g, 3.44 mmol) and CH_2Cl_2 (12 mL) is added NBS (0.64 g, 3.62 mmol). The solution was stirred overnight at ambient temperature, washed with water (2 x 75 mL), brine (75 mL), dried over Na_2SO_4 , filtered and concentrated to give the title compound (1.36 g, 3.29 mmol, 95%). $^1\text{H NMR}$ (CDCl_3), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.49 (s, 3H), 2.53 (s, 3H), 3.25-3.36 (m, 1H), 6.70 (s, 1H), 7.07 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 412.1; ANALYSIS: 412.0.

Example 85

3- [3-Chloro-5- (6-methyl-pyridin-2-yl) -thiophen-2-yl] -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] Preparation of pyridazine

Method A

3- (5-Bromo-3-chloro-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 73 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.027 g, 0.036 mmol) are added a 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (2.9 mL, 1.45 mmol). The mixture is stirred overnight at 65 ° C, diluted with EtOAc (50 mL), washed with saturated NH_4Cl (40 mL), water (40 mL), brine (40 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (20% to 40% EtOAc / hexane gradient) to yield the title compound (0.072 g, 0.17 mmol, 23%). $^1\text{H NMR}$ (CDCl_3), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.58 (s, 3H), 3.30-3.39 (m, 1H), 6.70 (s, 1H), 7.06 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.60 (dd, J = 7.7, 7.5 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 425.2; ANALYSIS: 425.2.

Method B

A 2- (4-Chloro-thiophen-2-yl) -6-methyl-pyridine-2-bromo-4-chloro-thiophene (Gronowitz, Rosen Chemical Scripts, 1971, 1, 33) (1.50 g, 7.60 mmol) solution and THF (25.00 mL, 11.39 mmol) in 0.5 M solution of 6-methyl-2-pyridyl zinc bromide, adding $\text{Pd}(\text{PPh}_3)_4$ (0.18 g, 0.15 mmol). The solution is heated at 40 ° C, overnight, diluted with Et₂O (50 mL), washed with saturated NH_4Cl (40 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (5% to 20% EtOAc / hexane gradient) to yield the title compound (0.45 g, 2.15 mmol, 28%). $^1\text{H NMR}$ (CDCl_3), δ 2.56 (s, 3H), 7.02 (d, 7.7 Hz, 1H), 7.13 (d, J = 0.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 0.9 Hz, 1H), 7.54 (dd, J = 7.9, 7.7, 1H).

B. 2- (5-Bromo-4-chloro-thiophen-2-yl) -6-methyl-pyridine-2- (4-chloro-thiophen-2-yl) -6-methyl-pyridine (Example Wrap-96) (To a 0 ° C. solution of 0.45 g, 1.45 mmol) and CH_2Cl_2 (10 mL) is added Br_2 (0.15 mL, 2.91 mmol). The solution is warmed to ambient temperature and stirred for 1 hour. The solution was washed with saturated NaHCO_3 (10 mL), saturated $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), dried over MgSO_4 , filtered and concentrated to give the title compound (0.59 g, 2.04, 95%). Is generated. $^1\text{H NMR}$ (CDCl_3), δ 2.55 (s, 3H), 7.05 (d, 7.9 Hz, 1H), 7.29 (s, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.58 (dd, J = 7.9, 7.9, 1H). LC / MS (m / z): Calculated C₁₉H₁₇BrClNS (M + H)⁺: 288.0; Analytical value: 287.9.

C. 3- [3-Chloro-5- (6-methyl-pyridin-2-yl) -thiophen-2-yl] -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine 8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.39 g, 1.78 mmol), 2- (5-bromo-4-chloro-A solution of thiophen-2-yl) -6-methyl-pyridine (0.59 g, 2.04 mmol), Cs_2CO_3 (1.23 g, 3.77 mmol) and DMF (5 mL)) was added with N_2 for 15 min. Degas. PPh_3 (0.089 g, 0.34 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.079 g, 0.86 mmol) are added and the solution is heated at 110 ° C. for 48 hours. The solution is diluted with EtOAc (30 mL), washed with saturated NH_4Cl (25 mL), dried over MgSO_4 , filtered and concentrated. The residue was purified by ISCO column chromatography (20-30% EtOAc / hexane gradient) and chromatographed (19 x 300 C18 Symmetry column, 20-45% water: 0.1% TFA / ACN: 0.1% TFA gradient) to yield the title compound (0.078 g, 0.18 mmol, 10%). Same spectrum as Method A.

Example 86

Preparation of 3- (3-chloro-5-pyridin-3-yl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine

Method A

3- (5-Bromo-3-chloro-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25 g, 61 mmol), (pyridine-3-boronic acid (0.082 g, 0.67 mmol), 2M Na_2CO_3 (0.45 mL, 0.91 mmol) and n-PrOH (1 mL) with nitrogen for 10 min. Degas $\text{Pd}(\text{OAc})_2$ (0.0027 g, 0.0012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added and the solution is heated overnight at 88 ° C. The solution is EtOAc (15 mL), in diluted water (10 mL), washed with saturated NaHCO_3 (10 mL), dried through MgSO_4 , filtered, ISCO column chromatography (1 concentrated And purified by 40% EtOAc / hexanes gradient) to produce the title compound (0.095g, 0.23mmol, 38%). $^1\text{H NMR}$ (CDCl_3), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.32-7.37 (m, 2H), 7.55-7.90 (m, 1H), 8.57 (d, J = 4.0 Hz, 1H), 8.89 (s, 1H). LC / MS (m / z): Calculated C₂₂H₂₃ClN₄S (M + H)⁺: 411.2; Analytical value: 411.2.

Method B

A. 3- (4-Chloro-thiophen-2-yl) -pyridine-2-bromo-4-chloro-thiophene (Gronowitz, Rosen Chemical Scripts, 1971, 1, 33) (1.45 g, 7.34 mmol), pyridine-3-boronic acid (0.99g, 7.71mmol), Na_2CO_3 of 2M (5.50mL, 11.01mmol) and a solution of n-PrOH (3mL), to 10 minutes degassing with N_2 . $\text{Pd}(\text{OAc})_2$ (0.033 g, 0.15 mmol) and PPh_3 (0.12 g, 0.44 mmol) were added and the solution was heated at 85 ° C. for 48 hours and diluted with CH_2Cl_2 (50 mL). Wash with 10% Na_2CO_3 (2 x 30 mL), dry over MgSO_4 , filter and concentrate. The residue is purified by ISCO column chromatography (20% to 30% EtOAc / hexane gradient) to yield the title compound (0.74 g, 3.78 mmol,

51%); ^1H NMR (CDCl_3), δ 7.12-7.13 (m, 1H), 7.20 (d, J = 1.4 Hz, 1H), 7.31 (dd, J = 8.0, 4.9 Hz, 1H), 7.78-7.82 (m, 1H), 8.55 (d, J = 4.9 Hz, 1H), 8.82 (d, J = 2.2 Hz, 1H).

B. 3-(5-Bromo-4-chloro-thiophen-2-yl)-pyridine Example 85 Method B Using a procedure analogous to step B, 3-(4-chloro-thiophen-2-yl)-pyridine (0.74 g, 3.78 mmol) and Br_2 (0.39 mL, 7.56 mmol) produce the title compound (0.99 g, 3.61 mmol, 95%). ^1H NMR (CDCl_3), δ 7.13 (s, 1H), 7.34 (dd, J = 8.1, 4.4 Hz, 1H), 7.74-7.78 (m, 1H), 8.58 (d, J = 4.4 Hz, 1H), 8.78 (s, 1H).

C. 3-(3-Chloro-5-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine Example 85 Method B Using a procedure analogous to step C, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.50 g, 2.33 mmol), 3-(5-bromo-4-chloro-thiophen-2-yl)-pyridine (0.76 g, 2.76 mmol), CaH_2 (0.11 g, 4.83 mmol), PPh_3 (0.11 g, 0.44 mmol) and $\text{Pd}(\text{DBA})_2$ (0.10 g, 0.11 mmol) to yield the title compound. The residue is purified by ISCO column chromatography (15-30% EtOAc / hexane gradient) to yield the title compound (0.35 g, 0.85 mmol, 37%). Same spectrum as Method A.

Example 87

Of 3-(3-Chloro-5-(4-fluoro-phenyl)-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation

Using a procedure analogous to Example 25, 3-(5-Bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25g, 0.51 mmol), 4-fluorophenylboronic acid (0.93g, 0.87 mmol), Na_2CO_3 of 2M (0.45 mL, 0.91 mmol), n-PrOH (2 mL), $\text{Pd}(\text{OAc})_2$ (0.0068 g, 0.030 mmol) and PPh_3 (0.016 g, 0.061 mmol) produce the title compound (0.041 g, 0.096 mmol, 16%). ^1H NMR (CDCl_3), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.79 (s, 1H), 7.07-7.13 (m, 2H), 7.22 (s, 1H), 7.54-7.60 (m, 2H). LC / MS (m/z): calcd (C₂₃H₂₃ClF₂N₅S) (M + H)⁺: 428.2; ANALYSIS: 428.1.

Example 88

3-(3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl)-8-(1-ethyl-propyl)-2 of 1,6-dimethyl-imidazo [1,2-b] pyridazine

Method A

A solution of 1-methyl-1,2,4-triazole (0.18 mL, 2.33 mmol) and THF (3 mL) at -78 °C was added n-Bu in hexane (1.49 mL, 2.33 mmol). Add a 1.56M solution of I.I. The solution is stirred at -78 °C for 30 minutes, a 0.5 M solution of ZnCl_2 in THF (4.78 mL, 2.33 mmol) is added and the solution is warmed to ambient temperature. 3-(5-Bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.32 g, 78 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.028 g, 0.039 mmol) were added and the solution was heated at 60 °C for 2 days, diluted with EtOAc (50 mL), saturated NH_4Cl (30 mL), water (30 mL), brine (30 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (20% to 10% EtOAc / hexane gradient) to yield the title compound (0.19 g, 0.46 mmol, 59%). ^1H NMR (CDCl_3), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.37 (m, 1H), 4.16 (s, 3H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H). LC / MS (m/z): calcd (C₂₀H₂₃ClN₅S) (M + H)⁺: 415.2; ANALYSIS: 415.1. Method B. A 5 L reaction flask equipped with a cooling bath, air stirrer, gas dispersion tube and thermometer probe was added to 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-1H-1,2,4-triazole (162.0 g, 0.745 mol), 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (250.1 g), 0.898 mol, NMP (800 mL), KOAc (366.0 g), TBABr (50.5 g) and additional NMP (700 mL) to form a mixture. Stirring while bubbled for one hour with N_2 mixture. A portion of a mixture of $\text{Pd}(\text{OAc})_2$ (8.37 g) and TBABr (24.55 g) is added and then heated at 120 °C for 3 hours. The reaction is cooled to 50 °C and transferred to a 12 L flask. The mixture is cooled to 20-25 °C and then added deionized H_2O (3.5 L) is added dropwise and allowed to stir overnight to precipitate a sticky solid that gradually solidifies. The solid is filtered, washed with deionized H_2O (2 x 2 L) and dried on a filter plate for 30-60 minutes. The crude solid (595 g) is warmed to 30 °C with EtOAc (6.0 L) and then filtered through GFF paper to remove insoluble material. The filtrate is dried over Na_2SO_4 , treated with Darco (30.0 g), heated at 35 °C, filtered and concentrated to give a brown solid (432 g). The crude solid is eluted with a silica plug (1.0 kg) with CH_2Cl_2 (4.0 L) followed by EtOAc (16.0 L). Similar fractions are combined and concentrated in vacuo to approximately 6.0 L, then treated with Darco with stirring overnight. After filtering Darco through GFF paper, the filtrate is concentrated to a solid (336 g). The solid is crystallized from EtOAc: heptane (1:2) to yield the title compound as a pale yellow solid. (187 g, 60.5%, >98% area-% by reverse phase: Zorbax SB-C8, 4.6 mm x 250 mm, 5 microns, UV = 218 nm, flow rate 1.0 mL / min, dryer temperature 25 °C, isocratic: 30% water (0.1% TFA) and 70% AcCN.

Example 89

8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(3-methyl-5H-imidazol-4-yl)-thiophen-2-yl)-imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol), 1,34 M n-Bu-Li (0.80 mL, 1.07 mmol), 0.5 M ZnCl_2 in THF (2.14 mL, 1.07 mmol), From 5-Iodo-1-methyl-1H-imidazole (0.24 g, 1.22 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.037 g, 0.051 mmol), the title compound (0.061 g, 0.15 mmol, 15%). ^1H NMR (CDCl_3), δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.24-3.38 (m, 1H), 3.61 (s, 3H), 6.68 (s, 1H), 7.02 (s, 1H), 7.23 (s, 1H), 7.55 (s, 1H). LC / MS (m/z): calcd (C₂₂H₂₇N₅S) (M + H)⁺: 394.3; ANALYSIS: 394.2.

Example 90

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo [1,2-b] pyridazine

A. 4,4,5,5-tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2] dioxaborolane 3-bromo-2-methyl-thiophene (Saika et. El. Chem. Soc.Chem.Communication, 18, 1994, 2133; Steinkopf et.al., Justus Liebigs Ann. Chem., 513, 1934, 281; 5, 5, 4', 4', 5', 5'-octamethyl-[2,2'] bi[[1,3,2] dioxaborolanyl] (4.90 g, 19.26 mmol) and KOAc (5.20 g, 52.58 mmol) is degassed with N_2 for 15 min. $\text{PdCl}_2(\text{dppf})$ (0.70 g, 0.88 mmol) is added and the solution is stirred overnight at ambient temperature and warmed at 85 °C for 3 hours. Dilute the solution with water (200 mL) and extract with EtOAc (2 x 100 mL). The combined organic layers were washed with water (2 x 200 mL), brine (200 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO column chromatography (5% to 20% EtOAc / hexane gradient) to yield the title compound (1.52 g, 6.78 mmol, 39%). ^1H NMR (CDCl_3), δ 1.34 (s, 12H), 2.72 (s, 3H), 7.04 (d, J = 5.0 Hz, 1H), 7.22 (d, 5.0 Hz, 1H).

B. 2-Methyl-thiophene-3-boronic acid 4,4,5,5-tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2] dioxaborolane (1.52 g, 6.78 mmol), acetone (15 mL) and water (15 mL) are added NaIO_4 (2.90 g, 13.56 mmol). The solution is stirred at ambient temperature for 24 hours and then heated at reflux for 24 hours. The solution is concentrated, dissolved in EtOAc (1450 mL), washed with water (100 mL), dried over MgSO_4 , filtered and concentrated to give the title compound (0.75 g, 5.49 mmol, 78%). Generate. ^1H NMR (CDCl_3), δ 2.93 (s, 3H), 7.10 (d, J = 5.3 Hz, 1H), 7.51 (d, 5.3 Hz, 1H).

C. 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo [1,2-b] pyridazine (1.55 g, 4.80 mmol), 2-methylthiophene-3-boronic acid (0.76g, 6.28 mmol), 2M Na_2CO_3 (3.60 mL, 7.20 mmol) and n-PrOH (20 mL), to 10 minutes degassing with N_2 . $\text{Pd}(\text{OAc})_2$ (0.022 g, 0.096 mmol), PPh_3 (0.076 g, 0.29 mmol) is added and the solution is heated at 60 °C for 24 hours and then at 90 °C for 24 hours. The solution is concentrated, diluted with EtOAc (50 mL), washed with 10% Na_2CO_3 (40 mL), water (40 mL), brine (40 mL), dried over MgSO_4 , filtered and concentrated. To do. The residue is purified by ISCO column chromatography (10% to 15% EtOAc / hexane gradient) to yield the title compound (0.78 g, 2.49 mmol, 52%). ^1H NMR (CDCl_3), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.94 (m, 4H), 2.38 (s, 3H), 2.44 (s, 3H), 2.50 (s, 3H), 3.30-3.40 (m, 1H), 6.64 (s, 1H), 7.11 (d, J = 5.3 Hz, 1H), 7.25 (d, J = 5.3 Hz, 1H). LC / MS (m/z): calcd (C₁₈H₂₁N₅S) (M + H)⁺: 314.2; ANALYSIS: 314.2.

Example 91

Preparation of 3- (5-bromo-2-methyl-thiophen-3-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine

8- (1-ethyl-propyl) -2,6-dimethyl-3- (2-methyl-thiophen-3-yl) -imidazo [1,2-b] pyridazine 0.76 g, 2.42 mmol) and CH_2Cl_2 To a solution of Cl_2 (10 mL) is added NBS (0.60 g, 3.37 mmol). The solution is stirred at ambient temperature for 2 hours and concentrated. The solution is dissolved in Et_2O (30 mL), washed with water (3 x 30 mL), brine (30 mL), dried over MgSO_4 , filtered and concentrated to give the title compound (0.95 g, 2.42 mmol, 99%). $^1\text{H NMR}$ (CDCl_3), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.31 (s, 3H), 2.42 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (s, 1H). LC / MS (m / z): calcd (M + H) = 392.2; ANALYSIS: 392.1.

Example 92

Preparation of 8- (1-ethyl-propyl) -2,6-dimethyl-3- (2-methyl-5-phenyl-thiophen-3-yl) -imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 32, 3- (5-bromo-2-methyl-thiophen-3-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.20 g, 0.51 mmol), and $\text{PdCl}_2(\text{dppf})$ (0.019 g, 0.025 mmol) and THF (2.0 mL, 1.02 mmol) solution of 0.5M phenyl zinc iodides in Was purified by column chromatography (0-10% EtOAc / hexane gradient) and chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1% TFA). / ACN: 0.1% TFA gradient) to yield the title compound (0.081 g, 0.21 mmol, 41%). $^1\text{H NMR}$ (CDCl_3), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.40 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.32-3.41 (m, 1H), 6.66 (s, 1H), 7.23-7.30 (m, 1H), 7.32 (s, 1H), 7.34-7.41 (m, 2H), 7.57-7.63 (m, 2H). LC / MS (m / z): Calculated (M + H) = 390.2; ANALYSIS: 390.2.

Example 93

Of 8- (1-ethyl-propyl) -2,6-dimethyl-3- (2-methyl-5-thiazol-2-yl-thiophen-3-yl) -imidazo [1,2-b] pyridazine Preparation

Using a procedure similar to that in Example 32, 3- (5-bromo-2-methyl-thiophen-3-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.20 g, 0.51 mmol), from THF (8.1 mL, 4.05 mmol) in 0.5M 2-thiazolyl zinc bromide and $\text{PdCl}_2(\text{dppf})$ (0.019 g, 0.025 mmol) To yield the title compound (0.20 g, 0.50 mmol, 99%). $^1\text{H NMR}$ (CDCl_3), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.40 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.60 (s, 1H), 7.22 (d, J = 3.2 Hz, 1H), 7.52 (s, 1H), 7.75 (d, J = 3.2 Hz, 1H). LC / MS (m / z): calcd (M + H) = 397.1; ANALYSIS: 397.2.

Example 94

8- (1-Ethyl-propyl) -2,6-dimethyl-3- (2-methyl-5- (6-methyl-pyridin-2-yl) -thiophen-3-yl) -imidazo [1,2-b] Preparation of pyridazine

Using a procedure similar to that in Example 32, 3- (5-bromo-2-methyl-thiophen-3-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.24 g, 0.61 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.022 g, 0.031 mmol) and THF (3.7 mL, 1.84 mmol) solution of 6-methyl-2-pyridyl zinc bromide The title compound (0.086 g, 0.21 mmol, 34%) is produced from a 0.5 M solution of $^1\text{H NMR}$ (CDCl_3), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.39 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.57 (s, 3H), 3.31-3.40 (m, 1H), 6.65 (s, 1H), 6.97 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.50-7.56 (m, 2H). LC / MS (m / z): calcd (M + H) = 405.2; ANALYSIS: 405.2.

Example 95

Preparation of 8- (1-ethyl-propyl) -2,6-dimethyl-3- (3-methyl-5-pyrimidin-5-yl-thiophen-2-yl) -imidazo [1,2-b] pyridazine

Using a procedure similar to that in Example 74B, 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.20 g, 0.51 mmol), (5-pyrimidinyl) boronic acid (0.076 g, 0.61 mmol), 2M of Na_2CO_3 (0.36 mL, 0.76 mmol), $\text{Pd}(\text{OAc})_2$ (0.0013 g, 0.01 mmol), PPh₃ (0.0060 g, 0.031 mmol) and n-PrOH (2 mL), to produce the title compound (0.084 g, 0.21 mmol, 42%). $^1\text{H NMR}$ (CDCl_3), δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.17 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 3.26-3.35 (m, 1H), 6.69 (s, 1H), 7.74 (s, 1H), 8.95 (s, 2H), 9.10 (s, 1H). LC / MS (m / z): calcd (M + H) = 392.3; ANALYSIS: 392.2.

Example 96

3- [5- (3,5-Dimethyl-isoxazol-4-yl) -3-methyl-thiophen-2-yl] -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] Preparation of pyridazine

To a flask of 4-iodo-3,5-dimethyl-isoxazole (0.34 g, 1.53 mmol) was added a solution of 5 g / 100 mL of Rieke® zinc in THF (3 mL, 2.29 mmol). Added. The slurry was heated at reflux for 4 hours to fix the zinc and the solution was 3- (5-bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.76 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.028 g, 0.038 mmol). The solution is heated at 50 ° C. overnight, diluted with EtOAc (20 mL), washed with 0.1 M HCl (15 mL), water (15 mL), brine (15 mL), dried over MgSO_4 , filtered and concentrated. To do. The residue is purified by ISCO column chromatography (15-30% EtOAc / hexane gradient) to yield the title compound (0.22 g, 0.54 mmol, 71%). $^1\text{H NMR}$ (CDCl_3), δ 0.92 (t, J = 7.5 Hz, 6H), 1.78-1.96 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 2.53 (s, 3H), 2.56 (s, 3H), 2.61 (s, 3H), 3.33-3.42 (m, 1H), 6.72 (s, 1H), 6.98 (s, 1H). LC / MS (m / z): calcd (M + H) = 409.3; ANALYSIS: 409.2.

Example 97

Preparation of 8- (1-ethyl-propyl) -2,6-dimethyl-3- (3-methyl-5-pyrimidin-2-yl-thiophen-2-yl) -imidazo [1,2-b] pyridazine

3- (5-Bromo-3-methyl thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.76 mmol), 2-tributylstannyl-pyrimidine (0.34 g, 0.92 mmol) and THF (5 mL) were degassed with N_2 for 10 min, triphenylarsine (0.047 g, 0.15 mmol) and $\text{Pd}(\text{OAc})_2$ (0.035 g, 0.038 mmol) is added and the solution is heated at 55 ° C. for 48 hours and concentrated. The residue was purified by ISCO column chromatography (15% to 30% EtOAc / hexane gradient), dissolved in acetonitrile (20 mL), washed with hexane (3 x 20 mL), concentrated, and the title compound (0.097 g, 0.25 mmol, 32%). $^1\text{H NMR}$ (CDCl_3), δ 0.88 (t, J = 7.4 Hz, 6H), 1.74-1.92 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.08 (t, J = 4.8, 1H), 7.93 (s, 1H), 8.69 (s, 2H). LC / MS (m / z): calcd (M + H) = 392.3; ANALYSIS: 392.2.

Example 98

Preparation of 8- (1-ethyl-propyl) -2,6-dimethyl-3- (1,3,5-trimethyl-1H-pyrazol-4-yl) -imidazo [1,2-b] pyridazine

A. 1,3,5-trimethylpyrazole-4-boronic acid

To a dry flask is added 300 mg (1.59 mmol) 4-bromo-1,3,5-trimethylpyrazole to 4.0 mL THF. The mixture is cooled to -78 ° C. and 1 eq of n-BuLi (1.6 M) is added via syringe. The mixture is stirred for 1.5 hours and 0.19 mL of trimethylborate (1.06 eq) is added. The reaction mixture is stirred for 2 hours until the solution reaches -10 ° C., 1.5 mL of 5N HCl is added and stirred for 30 minutes longer. Extract the aqueous layer three times with ethyl acetate. The combined organic fertilizer is dried over MgSO_4 , filtered and evaporated to an oil. The oil is dissolved in methanol / dichloromethane and reprecipitated. The residue is triturated with acetone / ethyl acetate and then filtered to give the title compound as a 92.1 mg (37.5%) white solid. $^1\text{H NMR}$ ($\text{DMSO}-d_6$), δ 5.92 (s), 3.72 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H) ppm.

B. 8- (1-Ethyl-propyl) -2,6-dimethyl-3- (1,3,5-trimethyl-1H-pyrazol-4-yl) -imidazo [1,2-b] pyridazine 3-yl-Do 2,6-dimethyl-8- (1-ethyl-propyl) -imidazo [1,2-b] pyridazine (200 mg, 0.582 mmol), 1,3,5-trimethylpyrazole-4- Boronic acid (233 mg, 1.53 mmol), $\text{Pd}(\text{PPh}_3)_4$ (13.4 mg, 0.01 mmol) are mixed in a microwave pressure tube. Then 0.58 mL of 2N Na_2CO_3 and 3.0 mL of dimethoxyethane / H₂O / ethanol (7: 3: 2) solution are added. The mixture is heated in the microwave at 155 ° C. for 20 minutes. Water is added and the mixture is extracted four times with ethyl acetate. The combined organic fertilizer is dried over MgSO_4 , filtered, evaporated to a chromatographic residue

using hexane, 1:1 hexane: ethyl acetate, then 100% ethyl acetate to give the title compound as a yellow oil (6.4%) is obtained. ¹H-NMR (DMSO-d₆): δ 6.86 (s, 1H); 3.73 (s, 3H); 3.06-3.10 (m, 1H); 2.41 (s, 3H); 2.22 (s, 3H); 2.03 (s, 3H); 1.93 (s, 3H); 1.74-1.83 (m, 4H); 0.77 (t, J = 7.26 Hz, 6H) ppm. MS / ES + = 327 (100%, M + 2).

Example 99

Preparation of 2,6-dimethyl-8-(1-propyl-butyl)-3-(1,3,5-trimethyl-1H-pyrazol-4-yl)-imidazo [1,2-b] pyridazine
3-Iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo [1,2-b] pyridazine (75 mg, 0.20 mmol), 1,3,5-trimethylpyrazole-4-boronic acid (80 mg, 0.52 mmol), 2N Na₂CO₃ solution (0.22 mL) and 5.0 mg (0.0604 mmol) of Pd (PPh₃)₄ were added to 1.5 mL of dimethyl ether / H₂O / ethanol-Mix in a microwave pressure vessel with a 7:3:2 solution. The mixture is heated in the microwave at 140 ° C. for 25 minutes. The mixture is evaporated and chromatographed on a silica gel column with hexane, 3:1 hexane: ethyl acetate, then 1:1 hexane: ethyl acetate to give the title compound (22.8%) as a clear oil. ¹H-NMR (DMSO-d₆): δ 6.88 (s, 1H); 3.72 (s, 3H); 3.06-3.10 (m, 1H); 2.40 (s, 3H); 2.21 (s, 3H); 2.02 (s, 3H); 1.92 (s, 3H); 1.69-1.76 (m, 4H); 1.08-1.21 (m, 4H); 0.82 (t, J = 7.49 Hz, 6H) ppm. MS / ES + = 354 (100%, M + 1).

Example 100

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophene-2-carboxylic acid dimethylamide
Using a procedure analogous to Example 23B, 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methylthiophene-2-carboxylic acid (161 mg, 0.42 mmol, 100%) is produced from 2-carboxylic acid (151 mg, 0.42 mmol) and 2.0 M dimethylamine (2.0 mL, 4 mmol). ¹H NMR (CDCl₃): δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.94 (m, 4H), 2.14 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.15-3.50 (m, 7H), 6.72 (s, 1H), 7.39 (s, 1H). ES MS (m / z): Calculated value C₂₁H₂₈N₄O₃ (M + H) +: 385.6 Analytical value: 385.3.

Example 101

8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-1H-imidazol-5-yl)-thiophen-2-yl]-imidazo [1,2-b] pyridazine Preparation of 1,2-b] pyridazine
Using a procedure similar to that in Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 1.02 mmol), 1.34 M n-BuLi (0.80 mL, 1.07 mmol), 0.5 M ZnCl₂ in THF (2.14 mL, 1.07 mmol), 3-From Iodo-1-methyl-1H-imidazole (0.24 mL, 1.22 mmol) and PdCl₂ (dppf) (0.037 g, 0.051 mmol), the title compound (0.030 g, 0.076 mmol, 8%). ¹H NMR (CDCl₃): δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.13 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.31-3.40 (m, 1H), 3.72 (s, 3H), 6.65 (s, 1H), 7.09 (d, J = 1.3 Hz, 1H), 7.19 (s, 1H), 7.85 (d, J = 1.3 Hz, 1H). LC / MS (m / z): calcd (M + H) +: 394.2; ANALYSIS: 394.2.

Example 102

N-(4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl)-morpholine (hydrochloride salt) Preparation of morpholine (hydrochloride salt)
IPA (225.0 mL) was added to the compound N-(4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl)-morpholine (18.8 g, 0.0448 mmol, below). The starting material slurry is heated on a Buchi bath at 50 ° C. to obtain a cloudy solution. Concentrated (12M) aqueous HCl (3.73 mL, 0.0448 mmole, 1.0 eq) was added in one portion and the cloudy solution was stirred on a Buchi at 50 ° C. for 10 minutes, then vacuum Evaporate down to a yellow solid. After 20 minutes at room temperature under vacuum (weight 20.9 g), acetone (100 mL) is added and the resulting yellow slurry is stirred at room temperature for 1 hour, then cooled in an ice bath and stirred for an additional hour. The slurry is filtered, rinsed with acetone, and dried under vacuum at 40 ° C. overnight to give 19.18 g (94%) of a pale yellow white crystalline solid. ¹H NMR (DMSO): δ 7.52 (s, 1H), 3.73 (t, J = 4.6 Hz, 4H), 3.49 (t, J = 5.2 Hz, 4H), 3.9 (m, 1H), 2.57 (s, 3H), 2.49 (s, 3H), 1.77 (m, 4H), 0.80 (t, J = 7.4 Hz, 6H).

Example 103

Of 8-(1-ethyl-propyl)-3-[5-(2-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation
Using a procedure similar to Example 30B, 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.18 g, 0.50 mmol), 1-bromo-2-fluoro-benzene (0.072 g, 0.55 mmol) and 2M Na₂CO₃ (0.38 mL, 0.76 mmol), n-PrOH (2 mL) and Pd (PPh₃)₄ (0.029 g, 0.025 mmol) produce the title compound (0.022 g, 0.054 mmol, 11%). ¹H NMR (CDCl₃): δ 0.93 (t, J = 7.4 Hz, 6H), 1.71-1.96 (m, 4H), 2.19 (s, 3H), 2.66 (s, 3H), 2.67 (s, 3H), 3.41-3.50 (m, 1H), 7.15 (s, 1H), 7.15-7.23 (m, 2H), 7.28-7.35 (m, 1H), 7.45 (d, J = 1.4 Hz, 1H), 7.66 (dt, J = 7.6, 1.6 Hz, 1H). LC / MS (m / z): calcd (M + H) +: 408.2; ANALYSIS: 408.2.

Example 104

Preparation of 3-(3-chloro-5-pyrimidin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
A 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine 3-(3-chloro-78 of -thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (2.0 g, 5.97 mmol) and THF (30 mL). To the solution at 0 ° C. 1.6 M n-BuLi (4.1 mL) is added. After 30 minutes, B (OMe)₃ (0.74 mL, 5.99 mmol) is added and the solution is warmed to ambient temperature and stirred overnight. 1M HCl (30 mL) is added and the solution is stirred for 20 minutes. The solution is made basic with 5M NaOH. The organic layer is extracted with 1M NaOH (30 mL). The composite aqueous layer is acidified with 5M HCl, K₃PO₄·3H₂O is added and the pH is adjusted to 5.5 with 1M NaOH. The combined aqueous layer is extracted with EtOAc (200 mL), washed with brine (150 mL), dried over MgSO₄, filtered and concentrated to yield the title compound (2.20 g, 5.82 mmol, 97%). To do. LC / MS (m / z): calcd (M + H) +: 378.7; ANALYSIS: 378.0.

8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-chloro-5-pyrimidin-2-yl-thiophen-2-yl)-imidazo [1,2-b] pyridazine 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25 g, 0.66 mmol) A solution of 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2M Na₂CO₃ (0.66 mL, 1.32 mmol) and i-PrOH (3 mL) is degassed with N₂ for 15 min. Pd (OAc)₂ (7.4 mg, 0.033 mmol) and PPh₃ (0.026 g, 0.099 mmol) are added and the solution is heated at 90 ° C. overnight. The solution is diluted with EtOAc (35 mL), washed with 10% Na₂CO₃ (35 mL), brine (35 mL), dried over Na₂SO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (20% to 30% EtOAc / hexane gradient) to yield the title compound (0.077 g, 0.19 mmol, 29%). ¹H NMR (CDCl₃): δ 0.88 (d, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.27-3.40 (m, 1H), 6.71 (s, 1H), 7.15 (t, J = 5.0 Hz, 1H), 8.00 (s, 1H), 8.74 (d, J = 5.0 Hz, 2H). LC / MS (m / z): calcd (M + H) +: 412.1; ANALYSIS: 412.2.

Example 105

Of 3-(3-chloro-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation
Using a procedure similar to that in Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25 g, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2M Na₂CO₃ (0.66 mL, 1.32 mmol) and i-PrOH (3 mL), Pd (OAc)₂ (7.4 mg, 0.033 mmol) and PPh₃ (0.026 g, 0.099 mmol) to yield the title compound (0.099 g, 0.24 mmol, 35%). ¹H NMR (CDCl₃): δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.35 (m, 1H), 6.71 (s, 1H), 7.33 (t, J = 3.3 Hz, 1H), 7.49 (s, 1H), 7.81 (d, J = 3.3 Hz, 2H). LC / MS (m / z): calcd (M + H) +: 417.1; ANALYSIS: 417.1.

Example 106

3-[3-chloro-5-(2-methyl-2H-pyrazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation of 1,2-b] pyridazine
To a -78 ° C. solution of 1-methyl-1H-pyrazol (0.12 g, 1.45 mmol) and THF (4 mL) is added 1.6 M n-BuLi (0.91 mL, 1.45 mmol). After 45 minutes, 0.5 M ZnCl₂ (2.9 mL, 1.45 mmol) is added and the solution is warmed to ambient temperature. After 30 minutes, 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo

[1,2-b] pyridazine (Example) Wrap 88) (0.30 g, 0.73 mmol) and PdCl₂ (dppf) (0.027 g, 0.036 mmol) were added and the solution was heated at 65 ° C. overnight, diluted with EtOAc (30 mL), saturated Wash with NH₄ Cl (2 x 30 mL), dry over MgSO₄, filter and concentrate. The residue is purified by ISCO column chromatography (15% to 30% EtOAc / hexane gradient) to yield the title compound (0.15 g, 0.36 mmol, 50%). ¹H NMR (CDCl₃) δ 9.88 (d, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 6H), 3.26- 3.36 (m, 1H), 4.05 (s, 3H), 6.45 (d, J = 1.9 Hz, 1H), 6.71 (s, 1H), 7.14 (s, 1H), 7.49 (d, J = 1.9 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 414.2; ANALYSIS: 414.2.

Example 107

Preparation of 3- (3-chloro-5-pyridin-4-yl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine
Using a procedure similar to that of Example 104, 3- (3-chloro-thiophen-2-yl-5-boronic acid) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25 g, 0.66 mmol), 4-bromo-pyridine hydrochloride (0.26 g, 1.32 mmol), 2M Na₂ CO₃ (1.00 mL, 1.99 mmol), i-PrOH (3 mL), Pd (OAc)₂ (7.4 mg, 0.033 mmol) and PPh₃ (0.026 g, 0.099 mmol) produce the title compound (0.16 g, 0.59 mmol, 59%). ¹H NMR (CDCl₃) δ 9.87 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 6.72 (s, 1H), 7.45-7.49 (m, 3H), 8.63 (d, J = 1.3 Hz, 1H), 8.64 (d, J = 1.3 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 411.1; ANALYSIS: 411.1.

Example 108

3- [3-Chloro-5- (3,5-dimethyl-isoxazol-4-yl) -thiophen-2-yl] -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine
Preparation of 1,2-b] pyridazine
Using a procedure similar to that in Example 104, 3- (3-chloro-thiophen-2-yl-5-boronic acid) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25 g, 0.66 mmol), 4-iodo-3,5-dimethyl-isoxazole (0.30 g, 1.32 mmol), 2M Na₂ CO₃ (0.66 mL, 1.32 mmol) and i-PrOH (3 mL), Pd (OAc)₂ (7.4 mg, 0.033 mmol) and PPh₃ (0.026 g, 0.099 mmol) from the title compound (0.14 g, 0.50 mmol, 50%). ¹H NMR (CDCl₃) δ 9.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.43 (s, 3H), 2.53 (s, 6H), 2.57 (s, 3H), 3.27-3.36 (m, 1H), 6.71 (s, 1H), 7.01 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 429.2; ANALYSIS: 429.2.

Example 109

Preparation of 3- (3-Chloro-5-pyridin-2-yl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine
3- (5-Bromo-3-chloro-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25 g (0.61 mmol) and PdCl₂ (dppf) (0.022 g, 0.030 mmol), a 0.5 M solution of 2-pyridylzinc bromide (2.40 mL, 1.21 mmol) was added at 65 ° C. overnight. Heat, dilute with EtOAc (30 mL), wash with saturated NH₄ Cl (2 x 30 mL), dry over MgSO₄, filter and concentrate. The residue is purified by ISCO column chromatography (20% -40%). % of clarified by EtOAc / hexanes gradient, then recrystallized from CH₃ CN, generate the title compound (0.15 g, 0.36 mmol, 60%). ¹H NMR (CDCl₃) δ 9.88 (d, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.17-7.23 (m, 1H), 7.56 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.70-7.76 (m, 1H), 8.59 (d, J = 4.7 Hz, 1H). LC / MS (m / z): calculated value C₂₂H₂₃ClN₄S (M + H)⁺: 412.0; analysis value: 412.4.

Example 110

Preparation of 3- (3-chloro-5-pyrimidin-5-yl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine
Using a procedure similar to that of Example 104, 3- (3-chloro-thiophen-2-yl-5-boronic acid) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25g, 0.66mmol), 4-bromo-pyrimidine (0.21g, 1.32mmol), 2M Na₂ CO₃ (0.66mL, 1.32mmol), i-PrOH (3mL), Pd (OAc)₂ (7.4 mg, 0.033 mmol) and PPh₃ (0.026 g, 0.099 mmol) to yield the title compound (0.053 g, 0.13 mmol, 20%). ¹H NMR (CDCl₃) δ 9.88 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.27-3.37 (m, 1H), 6.73 (s, 1H), 7.40 (s, 1H), 8.97 (s, 2H), 9.18 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 412.1; ANALYSIS: 411.2.

Example 111

Preparation of 3- (3-chloro-5-pyrazin-2-yl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine
Using a procedure similar to that of Example 104, 3- (3-chloro-thiophen-2-yl-5-boronic acid) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g (1.06 mmol), 2-iodo-pyrazine (0.16 g, 1.59 mmol), 2M Na₂ CO₃ (1.06 mL, 2.12 mmol) and i-PrOH (5 mL), Pd (OAc)₂ (0.012 g, 0.053 mmol) and PPh₃ (0.042 g, 0.16 mmol) produce the title compound (0.15 g, 0.36 mmol, 34%). ¹H NMR (CDCl₃) δ 9.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.25-3.37 (m, 1H), 6.71 (s, 1H), 7.66 (s, 1H), 8.45 (d, J = 2.6 Hz, 1H), 8.51-8.53 (m, 1H), 8.96 (d, J = 1.0 Hz, 1H). LC / MS (m / z): Calculated value C₂₁H₂₂ClN₅S (M + H)⁺: 412.1 Analytical value: 412.3.

Example 112

Of 3- (3-chloro-5-thiazol-4-yl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine Preparation
3- (5-Bromo-3-chloro-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.60 g, 1.1 To a 0 ° C. solution of 45 mmol) and THF (2 mL) is added 0.95 g / mL Reiki® Zn (3.80 mL, 2.91 mmol). The solution is refluxed and heated for 1 hour; and excess Zn is fixed at room temperature for 1 hour. The solution is transferred to a flask of 4-bromo-thiazol (ethyl, T. et al. Tetrahedron Lett. 1995, 51, 9293) (0.29 g, 1.74 mmol). PdCl₂ (dppf) (0.027 g, 0.036 mmol) is added and the solution is heated at 65 ° C. overnight, diluted with EtOAc (40 mL), washed with saturated NH₄ Cl (30 mL) and dried over MgSO₄. Filter and concentrate. The residue was purified by ISCO column chromatography (15-20% EtOAc / hexane gradient) and then by ISCO column chromatography (100% Et₂O) to give the title compound (0.098 g, 0.24 mmol, 16%). ¹H NMR (CDCl₃) δ 9.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.70 (s, 1H), 7.45 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 8.85 (d, J = 2.0 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 417.1; ANALYSIS: 417.3.

Example 113

8- (1-Ethyl-1-fluoro-propyl) -2,6-dimethyl-3- [3-methyl-5- (6-methyl-pyridin-2-yl) -thiophen-2-yl] -imidazo [1,2-b] pyridazine
Preparation of 1,2-b] pyridazine
3- (2,6-Dimethyl-3- [3-methyl-5- (6-methyl-pyridin-2-yl) -thiophen-2-yl] -imidazo [1,2-b] pyridazin-8-yl) -Pentane-3-ol (0.23 g, 0.55 mmol) and CH₂ Cl₂ (3 mL) in a -78 ° C. solution with [bis (2-methoxyethyl) amino] sulfur trifluoride (0.14 g, 0.60 mmol) and a solution of CH₂ Cl₂ (2 mL). The solution is warmed to ambient temperature and stirred overnight. The solution is washed with saturated NaHCO₃ (5 mL) and concentrated. The residue is purified by ISCO column chromatography (15% to 20% EtOAc / hexane gradient) to yield the title compound (0.13 g, 0.31 mmol, 57%). ¹H NMR (CDCl₃) δ 9.80 (t, J = 7.5 Hz, 6H), 2.14 (s, 3H), 2.16-2.31 (m, 2H), 2.46 (s, 3H), 2.54 (s, 3H), 2.56 (s, 3H), 2.59-2.70 (m, 2H), 6.98 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 7.8, 7.6 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 423.2; ANALYSIS: 423.4.

Example 114

Preparation of 2- [8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl] -thiophene-3-carbonitrile

To a 0.55 g / mL solution of Reike® Zn (31 mL, 23.93 mmol) was added 2-bromo-thiophene-3-carbonitrile (Fournier, P. et al. Bull. Soc. Chim. Fr., 1967, 4115) (2.25 g, 11.95 mmol) and THF (5 mL) are added. The solution is refluxed and heated for 2 hours and cooled to room temperature to fix the excess Zn. The solution was washed with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine (2.5 g, 7.98 mmol) and PdCl₂ (dppf) (0.29 g, 0.940 mmol) is transferred via cannula. The mixture is heated at 65 ° C. overnight, diluted with EtOAc (75 mL), washed with saturated NH₄ Cl (2 × 75 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (10% to 20% EtOAc / hexane gradient) to yield the title compound (1.10 g, 3.39 mmol, 42%). ¹H NMR (CDCl₃) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.55 (s, 3H), 2.61 (s, 3H), 3.25-3.34 (m, 1H), 6.75 (s, 1H), 7.35 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 5.2 Hz, 1H). LC / MS (m / z): Calculated C₁₈H₂₀N₄S (M + H)⁺: 325.5; Analytical value: 325.2.

Example 115

Preparation of 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiophene-3-carbonitrile
2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiophene-3-carbonitrile (0.83 g, 2.56 mmol) and To a solution of CH₂Cl₂ (10 mL) is added NBS (0.48 g, 2.69 mmol). The solution was stirred for 1 h, diluted with Et₂O (100 mL), washed with water (3 × 100 mL), brine (100 mL), filtered, dried (MgSO₄), filtered, concentrated. This yields the title compound (1.03 g, 2.55 mmol, 99%). ¹H NMR (CDCl₃) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.55 (s, 3H), 2.60 (s, 3H), 3.24-3.32 (m, 1H), 6.75 (s, 1H), 7.30 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 404.4; ANALYSIS: 404.1.

Example 116

2-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile Preparation of
5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and PdCl₂ (dppf) (0.023 g, 0.031 mmol) are added to a solution of 0.5 M 2-thiazolylzinc bromide (6.0 mL, 3.10 mmol). The solution is heated at 65 ° C. overnight, diluted with EtOAc (30 mL), washed with saturated NH₄ Cl (2 × 25 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (15-20% EtOAc / hexane gradient) to yield the title compound (0.16 g, 0.39 mmol, 64%). ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3H), 2.66 (s, 3H), 3.25-3.35 (m, 1H), 6.76 (s, 1H), 7.38 (d, J = 3.5 Hz, 1H), 7.70 (s, 1H), 7.84 (d, J = 3.5 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 408.6; ANALYSIS: 408.1.

Example 117

2-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile Preparation of
A solution of 1-methyl-1,2,4-triazole (0.14 mL, 1.86 mmol) and THF (5 mL) at -78 ° C. was added n-BuLi in hexane (1.20 mL, 1.86 mmol). A 1.6M solution of is added and after 30 minutes a 0.5M solution of ZnCl₂ in THF (4.70 mL, 2.33 mmol) is added, the solution is warmed to ambient temperature and stirred for 30 minutes. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiophene-3-carbonitrile (Example 1ap-122) (0.25 g, 0.62 mmol) and PdCl₂ (dppf) (0.023 g, 0.031 mmol) are added and the solution is heated at 65 ° C. overnight, diluted with EtOAc (25 mL) and saturated NH₄ Cl (20 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by ISCO column chromatography (15-60% EtOAc / hexane gradient) and chromatographed (50 × 250 C18 X-Terra RP column, 30-90% 10 mM NH₄ HCO₃ / water / 5% ACN; ACN gradient). The residue was dissolved in Et₂O (25 mL), washed with saturated NaHCO₃ (25 mL), dried over MgSO₄, filtered and concentrated to give the title compound (0.013 g, 0.032 mmol, 5%). Is generated. ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3H), 2.67 (s, 3H), 3.26-3.34 (m, 1H), 4.17 (s, 3H), 6.79 (s, 1H), 6.78 (s, 1H), 7.92 (s, 1H). LC / MS (m / z): Calculated value C₂₁H₂₃N₇S (M + H)⁺: 406.5; Analytical value: 406.2.

Example 118

2-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-5-(6-methyl-pyridin-2-yl)-thiophene-3-carbonitrile Preparation of 3-carbonitrile
5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and PdCl₂ (dppf) (0.023 g, 0.031 mmol) are added to a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.50 mL, 1.24 mmol) in a flask containing 62 mmol) and PdCl₂ (dppf) (0.024 g, 0.033 mmol). Add. The solution is heated at 65 ° C. overnight, diluted with EtOAc (30 mL), washed with saturated NH₄ Cl (2 × 30 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (15-25% EtOAc / hexane gradient) to yield the title compound (0.11 g, 0.26 mmol, 39%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.76-1.92 (m, 4H), 2.57 (s, 3H), 2.58 (s, 3H), 2.65 (s, 3H), 3.26-3.35 (m, 1H), 6.75 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 7.9, 7.5 Hz, 1H), 7.74 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 416.6; ANALYSIS: 416.2.

Example 119

Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-5-pyridin-3-yl-thiophene-3-carbonitrile
To a -78 ° C. solution of 3-iodo-pyridine (0.32 g, 1.56 mmol), 0.5 M ZnCl₂ in THF (3.20 mL, 1.59 mmol), and THF (2 mL), 7M t-BuLi (1.85 mL, 3.15 mmol) is added. The solution is warmed to ambient temperature and stirred for 30 minutes. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiophene-3-carbonitrile (0.21 g, 0.52 mmol) and Pd (PPh₃)₄ (0.03 g, 0.026 mmol) were added and the solution was heated at 55 ° C. for 1 h, cooled to ambient temperature, stirred overnight and diluted with EtOAc (50 mL). Washed with saturated NH₄ Cl (2 × 40 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (15-40% EtOAc / hexane gradient) to yield the title compound (0.15 g, 0.37 mmol, 71%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.58 (s, 3H), 2.66 (s, 3H), 3.26-3.35 (m, 1H), 6.76 (s, 1H), 7.34-7.46 (m, 1H), 7.56 (s, 1H), 7.91 (d, J = 7.1 Hz, 1H), 8.62 (s, 1H), 8.91 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 402.6; ANALYSIS: 402.4.

Example 120

Preparation of 3-(3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
A. 2,4-Dimethyl-thiophene (2.0 g, 17.82 mmol) in 2-bromo-3,4-dimethyl-thiophene CH₂Cl₂ (20 mL) (Minato et. Al., Tetrahedron 1982, 38, 3347) To the solution of NBS (3.3 g, 18.72 mmol) is added. The solution is stirred for 1 h, diluted with Et₂O (100 mL), washed with water (3 × 100 mL), brine (100 mL), dried (MgSO₄), filtered and concentrated. The residue is purified by ISCO column chromatography (100% hexane) to yield the title compound (3.0 g, 16.70 mmol). ¹H NMR (CDCl₃) δ 2.10 (s, 3H), 2.17 (s, 3H), 6.55 (s, 1H).
B. 3-(3,4-Dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3,4,3',4'-tetramethyl-[2,2'] bithiophenyl-5-yl)-imidazo [1,2-b] pyridazine 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (2.30 g, 10.58 mmol), 2-bromo-3,4-dimethyl-thiophene (3.03 g, 15.88 mmol) and Cs₂CO₃ (7.24 g, 22.23 mmol) and DMF (50 mL) are degassed with N₂ for 20 min. Pd₂(DBA)₃ (0.48 g, 0.053 mmol) and PPh₃ (0.56 g, 0.21 mmol) are added and the solution is heated at 120 ° C. overnight. The solution is diluted with EtOAc (200 mL), washed with water (3 × 200 mL), brine (200 mL), dried (MgSO₄), filtered and concentrated. The residue was purified by ISCO column chromatography (10% to 15% EtOAc / hexane gradient) to produce 2.04 g of red oil and

chromatographed (50 × 250 C18 Symmetry column, 30-70% water: 0.1% TFA / ACN gradient) to yield the title compound (0.41 g, 1.25 mmol, 12%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.94 (m, 4H), 2.00 (s, 3H), 2.24 (d, J = 1.0 Hz, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.65 (s, 1H), 7.10 (s, 1H). LC / MS (m / z): Calculated C₁₉H₂₅N₃S (M + H)⁺: 328.5; Analytical value: 328.3

Example 121

8- (1-Ethyl-propyl) -2,6-dimethyl-3- [3-methyl-4- (6-methyl-pyridin-2-yl) -thiophen-2-yl] -imidazo [1,2-b] Preparation of pyridazine

3- (4-Bromo-3-methyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (below) (0.25 g, 0.64 mmol) and PdCl₂ (dppf) (0.023 g, 0.032 mmol) in a 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.5 mL, 1.27 mmol). Add the solution. The solution is heated at 55 ° C. overnight, diluted with EtOAc (25 mL), washed with saturated NH₄Cl (20 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO (15% to 20% EtOAc gradient) and chromatographed (50 × 250 C18 Symmetry column, 10-70% water: 0.1% TFA / ACN: 0.1% TFA gradient). The residue was dissolved in Et₂O (20 mL), washed with saturated NaHCO₃ (15 mL), dried over MgSO₄, filtered and concentrated to give the title compound (0.066 g, 1.57 mmol, 31%). Is generated.

¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.20 (s, 3H), 2.47 (s, 3H), 2.49 (s, 3H), 2.61 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 7.5, 7.8 Hz, 1H), 7.72 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 405.2; ANALYSIS: 405.3.

Example 122

Preparation of 3- (5-bromo-3,4-dimethyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine

3- (3,4-Dimethyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.41 g, 1.25 mmol) and NBS (0.23 g, 1.32 mmol) is added to a solution of CH₂Cl₂ (30 mL). The solution was stirred for 1 h, diluted with Et₂O (100 mL), washed with water (3 × 100 mL), brine (100 mL), dried (MgSO₄), filtered and concentrated to give the title. This produces the compound (0.41 g, 1.01 mmol, 80%). ¹H NMR (CDCl₃) δ 0.86 (t, J = 7.4 Hz, 6H), 1.72-1.94 (m, 4H), 2.02 (s, 3H), 2.18 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 3.27-3.35 (m, 1H), 6.57 (s, 1H). LC / MS (m / z): Calculated C₁₉H₂₄BrN₃S (M + H)⁺: 407.4; Analytical value: 407.3.

Example 123

3- [3,4-Dimethyl-5- (2-methyl-2H- [1,2,4] triazol-3-yl) -thiophen-2-yl] -8- (1-ethyl-propyl) Preparation of -2,6-dimethyl-imidazo [1,2-b] pyridazine

A solution of 1-methyl-1,2,4-triazole (0.055 mL, 0.74 mmol) and THF (2 mL) at -78 ° C. was added n-BuLi in hexane (0.46 mL, 0.74 mmol). A 1.6 M solution of is added. Warm the solution to ambient temperature and stir for 30 minutes. Cool the solution to 0 ° C., add a 0.5 M solution of ZnCl₂ in THF (4.70 mL, 2.33 mmol), warm the solution to ambient temperature and stir for 30 min. 3- (5-Bromo-3,4-dimethyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.10 g, 0.25 mmol) and PdCl₂ (dppf) (0.009 g, 0.012 mmol) are added and the solution is heated at 55 ° C. overnight, diluted with EtOAc (25 mL) and washed with saturated NH₄Cl (20 mL). Dried over MgSO₄, filtered and concentrated. The residue was purified by ISCO column chromatography (15% -60% EtOAc / hexane gradient) followed by a second purification by ISCO column chromatography (100% Et₂O) to give the title compound (0.07 g, 0.17 mmol, 70%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3H), 2.29 (s, 3H), 2.47 (s, 3H), 2.51 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.69 (s, 1H), 8.00 (s, 1H). LC / MS (m / z): calcd (M + H)⁺: 409.6; ANALYSIS: 409.2.

Example 124

3- (3,4-Dimethyl-5-thiazol-2-yl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] Preparation of pyridazine

3- (5-Bromo-3,4-dimethyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.10 g, 0.25 mmol) and THF (1 mL) is added 1.6 M n-BuLi (0.16 mL). The solution is stirred for 45 min and 0.5M ZnCl₂ in THF (0.52 mL, 0.26 mmol) is added. The solution is warmed to ambient temperature and stirred for 30 minutes. 2-Bromo-thiazol (0.044 mL, 0.49 mmol) and PdCl₂ (dppf) (0.009 g, 0.012 mmol) were added and the solution was heated at 55 ° C. overnight and EtOAc (25 mL). Dilute, wash with saturated NH₄Cl (20 mL), dry over MgSO₄, filter and concentrate. The residue is purified by ISCO column chromatography (15% -20% EtOAc / hexane gradient) to yield the title compound (6.1 mg, 0.015 mmol, 6%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3H), 4.9 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.29-3.39 (m, 1H), 6.58 (s, 1H), 7.35 (d, J = 3.1 Hz, 1H), 7.86 (d, J = 3.1 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 411.6; ANALYSIS: 411.2.

Example 125

3- [3,4-Dimethyl-5- (6-methyl-pyridin-2-yl) -thiophen-2-yl] -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] Preparation of pyridazine

3- (5-Bromo-3,4-dimethyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.10 g, 0.25 mmol) and PdCl₂ (dppf) (9 mg, 0.012 mmol) was added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (0.98 mL, 0.49 mmol). To do. The solution is heated at 55 ° C. overnight, diluted with EtOAc (30 mL), washed with saturated NH₄Cl (30 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (15% -30% EtOAc / hexane gradient) to yield the title compound (0.029 g, 0.069 mmol, 29%). ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.04 (s, 3H), 4.5 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 2.59 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.0, 7.8 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 419.6; ANALYSIS: 419.4.

Example 126

3- [3,4-Dimethyl-5- (6-methyl-pyridin-2-yl) -thiophen-2-yl] -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] Preparation of pyridazine

To a -78 ° C. solution of 0.5 M ZnCl₂ 3-iodo-pyridine (0.15 g, 0.74 mmol) and THF (1.5 mL, 0.75 mmol) was added t-BuLi (0.88 mL, 1.49 mmol) is added. Warm the slurry to ambient temperature and stir for 30 minutes. 3- (5-Bromo-3,4-dimethyl-thiophen-2-yl) -8- (1-ethyl-propyl) -2,6-dimethyl-imidazo [1,2-b] pyridazine (0.10 g, 0.25 mmol) and PdCl₂ (dppf) (0.014 g, 0.012 mmol), stirred for 2 days the solution at room temperature, diluted with EtOAc (35 mL), washed with saturated NH₄Cl (30 mL). Dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (20% -30% EtOAc / hexane gradient) to yield the title compound (6.1 mg, 0.015 mmol, 6%). ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3H), 2.9 (s, 3H), 2.49 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.36 (dd, J = 8.0, 4.5 Hz, 1H), 7.79-7.83 (m, 1H), 8.57 (d, J = 4.5 Hz, 1H), 8.79 (d, J = 0.9 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 405.6; ANALYSIS: 405.2.

Examples 127 and 128

8- (1-ethyl-propyl) -3- (3-methoxy-thiophen-2-yl) -2,6-dimethyl-imidazo [1,2-b] pyridazine and 8- (1-ethyl-propyl) -Preparation of 3- (4-methoxy-thiophen-2-yl) -2,6-dimethyl-imidazo [1,2-b] pyridazine

Example 127

Example 128

Et₂O (50 mL) solution of 3-methoxy-thiophene (2.19 g, 19.14 mmol) in a solution of 1.5 M n-BuLi (12.20 mL, 19.46 mmol) is added. The solution is heated at reflux for 30 minutes and cooled to ambient temperature. A solution of 0.5 M ZnCl₂ (38.9 mL, 19.5 mmol) and THF (50 mL) is added and the solution is stirred for 30 minutes. 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine (2.0 g, 6.36 mmol) and PdCl₂(dppf) (0.23 g, 0.062 mmol) is added and the solution is heated at 65 ° C. for 4 h, diluted with EtOAc (250 mL), washed with saturated NH₄Cl (250 mL), dried over MgSO₄, filtered and concentrated. To do. The residue was purified by ISCO column chromatography (10% -25% EtOAc / hexane gradient) to give the title compound (1.50 g, 4.55 mmol, 71%) and (0.23 g, 0.70 mmol, 11%) respectively.

Example 127: ¹H NMR (CDCl₃) δ 0.83 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.59 (s, 3H), 2.70 (s, 3H), 3.26-3.35 (m, 1H), 3.86 (s, 3H), 6.32 (d, J = 1.6 Hz, 1H), 6.67 (s, 1H), 7.41 (d, J = 1.6 Hz, 1H). LC / MS (m / z): calcd C₁₈H₂₂N₄O (M + H)⁺: 330.5; ANALYSIS: 330.3.

Example 128: ¹H NMR (CDCl₃) δ 0.84 (t, J = 7.5 Hz, 6H), 1.71-1.88 (m, 4H), 2.47 (s, 3H), 2.49 (s, 3H), 3.26-3.35 (m, 1H), 3.84 (s, 3H), 6.62 (s, 1H), 6.96 (d, J = 5.5 Hz, 1H), 7.39 (d, J = 5.5 Hz, 1H). LC / MS (m / z): calcd C₁₈H₂₂N₄O (M + H)⁺: 330.5; ANALYSIS: 330.3.

Example 129

Preparation of 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
8-(1-Ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.78 g, 2.37 mmol) and CH₃Cl (10 mL), is added NBS (0.44 g, 2.49 mmol). The solution was stirred for 1 h, washed with water (3 × 10 mL), concentrated and purified by ISCO column chromatography (5% -15% EtOAc / hexane gradient) to give the title compound (0.87 g, 2.13 mmol, 90%). ¹H NMR (CDCl₃) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.26-3.35 (m, 1H), 3.82 (s, 3H), 6.65 (s, 1H), 6.97 (s, 1H). LC / MS (m / z): Calculated C₁₈H₂₂BrN₄O (M + H)⁺: 408.1; Analytical value: 408.3.

Example 130

8-(1-Ethyl-propyl)-3-(3-methoxy-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
Preparation of pyridazine
3-(5-Bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.20 g, 49 mmol) and PdCl₂(dppf) (0.018 g, 0.024 mmol) was added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.47 mmol). To do. The solution is heated at 65 ° C. overnight, diluted with EtOAc (30 mL), washed with saturated NH₄Cl (2 × 30 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (15% -20% EtOAc / hexane gradient) to yield the title compound (0.066 g, 1.57 mmol, 31%). ¹H NMR (CDCl₃) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.50 (s, 3H), 2.51 (s, 3H), 2.55 (s, 3H), 3.26-3.37 (m, 1H), 3.90 (s, 3H), 6.63 (s, 1H), 6.99 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.49 (s, 1H), 7.54 (dd, J = 7.4, 7.7 Hz, 1H). LC / MS (m / z): calcd C₂₂H₂₆N₄O (M + H)⁺: 421.6; ANALYSIS: 422.4.

Example 131

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-5-pyridin-3-yl-thiophen-2-yl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
To a -78 ° C. solution of 0.5 M ZnCl₂ in 3,4-dio-pyridine (0.32 g, 1.56 mmol) and THF (3.20 mL, 1.59 mmol) was added t-BuLi (2.27 mL, 3.85 mmol) is added. The solution is warmed to ambient temperature and stirred for 30 minutes. 3-(5-Bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.26 g, 64 mmol) and Pd(PPh₃)₄ (0.037 g, 0.032 mmol) are added and the solution is heated at 50 ° C. for 1 hour, cooled to ambient temperature and stirred overnight. The solution is diluted with EtOAc (50 mL), washed with saturated NH₄Cl (2 × 30 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (20% -50% EtOAc / hexane gradient) to yield the title compound (0.16 g, 0.39 mmol, 61%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 3H), 2.55 (s, 3H), 3.28-3.38 (m, 1H), 3.93 (s, 3H), 6.67 (s, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.31-7.36 (m, 1H), 7.68-7.92 (m, 1H), 8.55 (d, J = 4.5 Hz, 1H), 8.92 (d, J = 1.8 Hz, 1H). LC / MS (m / z): calcd C₂₂H₂₆N₄O (M + H)⁺: 407.6; ANALYSIS: 407.4.

Example 132

8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-4-yl-thiazol-5-yl)-imidazo [1,2-b] pyridazine (Of the hydrochloride salt)
3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (500 mg, 1.27 mmol), 4-pyridineboronic acid (500 mg, 4 mmol), Pd(PPh₃)₄ (100 mg, 0.08 mmol), toluene (2 mL), MeOH (1 mL) and K₂CO₃ (2M aqueous solution, 3.5 mL). The mixture is heated at 100 ° C. for 18 hours. Ethyl acetate (20 mL) is added and the organic layer is separated, dried over magnesium sulfate, filtered and concentrated in vacuo. Purification is performed via silica gel chromatography using a 3:1 mixture of hexane and ethyl acetate to give the free amine of the title compound (200 mg, 40%). The clarified product is decomposed with ethyl acetate and a freshly prepared solution of hydrogen chloride (0.5 M in ethyl acetate, 2 mL) is added. The solvent is removed in vacuo to give the title compound. ¹H NMR (CDCl₃) δ 8.2 (m, 2H), 7.65 (m, 2H), 6.55 (s, 1H), 3.24 (m, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 2.33 (s, 3H), 1.76 (m, 4H), 0.80 (t, 6H) ppm. MS / ES⁺ = 391 (100%, M + 1).

Example 133

8-(1-Ethyl-propyl)-3-(3-methoxy-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
A. Triazol of 5-bromo-1-methyl-1H-[1,2,4] 1-methyl-1H-[1,2,4] triazole (1.0 mL, 13.20 mmol) and THF (To a -78 ° C. solution of 100 mL) is added 1.5 M n-BuLi (8.70 mL, 13.86 mmol). After 45 minutes, 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over MgSO₄, filtered and concentrated to give the title compound (1.37 g, 8.46 mmol, 64%). Is generated. ¹H NMR (CDCl₃) δ 3.82 (s, 3H), 7.78 (s, 1H). LC / MS (m / z): Calcd C₂₁H₂₅N₅O (M + H)⁺: 162.0; ANALYSIS: 161.9.
B. 8-(1-Ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo [1,2-b] pyridazine 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.75 g, 2.28 mmol) and CH₃CN (10 mL) To the solution of is added NIS (0.54 g, 2.39 mmol). The solution was stirred overnight, concentrated, diluted with EtOAc (30 mL), washed with water (30 mL), saturated NH₄Cl (30 mL), 20% (NaHSO₃) (30 mL), brine (30 mL), MgSO₄ Dry through a filter and concentrate. The residue is purified by ISCO column chromatography (15% -20% EtOAc / hexane gradient) to yield the title compound (0.91 g, 2.00 mmol, 88%). ¹H NMR (CDCl₃) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.26-3.35 (m, 1H), 3.83 (s, 3H), 6.64 (s, 1H), 7.12 (s, 1H). LC / MS (m / z): calcd C₁₈H₂₂N₄O (M + H)⁺: 456.4; ANALYSIS: 456.0.

C. Triazol of 5-bromo-1-methyl-1H-[1,2,4] 1-methyl-1H-[1,2,4] triazole (1.0 mL, 13.20 mmol) and THF (To a -78 ° C. solution of 100 mL) is added 1.5 M n-BuLi (8.70 mL, 13.86 mmol). After 45 minutes, 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over MgSO₄, filtered and concentrated to give the title compound (1.37 g, 8.46 mmol, 64%). Is generated. ¹H NMR (CDCl₃) δ 3.82 (s, 3H), 7.78 (s, 1H). LC / MS (m / z): Calcd C₂₁H₂₅N₅O (M + H)⁺: 162.0; ANALYSIS: 161.9.

D. 8-(1-ethyl-propyl)-3-(3-methoxy-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl)-2,6-dimethylimidazo [1,2-b] pyridazine To a slurry of 0.05 g/mL Reiske® Zn in THF (2.8 mL, 2.11 mmol) was added 5-bromo-1-methyl-Add 1H-[1,2,4] triazole and THF (2 mL). The solution is heated at 65 °C. for 1 hour, cooled to room temperature, and excess Zn is fixed for 1 hour. The solution was dissolved in 8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.32 g, 0.70 mmol) and Pd(PPh₃)₄ (0.041 g, 0.035 mmol). The solution is heated at 65 °C. overnight, diluted with EtOAc (30 mL) and washed with saturated NH₄Cl (30 mL). The aqueous phase is extracted with EtOAc (20 mL). The combined organic layer is dried over MgSO₄, filtered and concentrated. The residue was purified by ISCO column chromatography (20% -65% EtOAc / hexane gradient), then purified by ISCO column chromatography (100% Et₂O) to give the title compound (0.19 g, 0.46 mmol, 62%).¹ H NMR (CDCl₃) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.92 (s, 3H), 4.15 (s, 3H), 6.67 (s, 1H), 7.48 (s, 1H), 7.89 (s, 1H). LC / MS (m / z): Calculated value C₂₁H₂₆N₆OS (M + H)⁺: 411.5; Analytical value: 411.3.

Example 134

Of 8-(1-ethyl-propyl)-3-(3-methoxy-5-thiazol-2-yl-thiophen-2-yl)-2,6-dimethylimidazo [1,2-b] pyridazine Preparation

8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.45 g, 0.99 mmol) and PdCl₂(dppf) (0.057 g, 0.078 mmol) are added to a 0.5 M solution of 2-thiazolylzinc bromide (9.9 mL, 4.94 mmol). The solution is heated at 65 °C. overnight, diluted with EtOAc (50 mL), washed with saturated NH₄Cl (50 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO column chromatography (15% -20% EtOAc / hexane gradient) to yield the title compound (0.29 g, 0.70 mmol, 71%).¹ H NMR (CDCl₃) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.51 (s, 3H), 2.53 (s, 3H), 3.28-3.37 (m, 1H), 3.93 (s, 3H), 6.67 (s, 1H), 7.28 (d, J = 3.3 Hz, 1H), 7.41 (s, 1H), 7.80 (d, J = 3.3 Hz, 1H). LC / MS (m / z): calcd (M + H)⁺: 413.6; ANALYSIS: 414.3.

0.19 g, 0.46 mmol

Example 135

Of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-morpholin-4-yl-thiazol-5-yl)-imidazo [1,2-b] pyridazine Preparation

110 mg 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.28 mmol) and 122 mg of morpholine (1.4 mmol) is dissolved in 3.0 mL of THF and 182 mg of cesium carboxylate (0.56 mmol) is added. The mixture is placed in a 4 mL vial with a Teflon lined cap and heated at 110 °C. overnight. The reaction mixture is concentrated and applied to a silica gel column chromatography column with hexane: EtOAc = 3: 1 eluent to yield 98 mg of the title compound (88%). Mass spectrum (m / e): 400 (M + 1);¹ H NMR (CDCl₃) δ 6.70 (s, 1H), 3.87 (t, 4H, J = 4.8 Hz), 3.56 (t, 4H, J = 4.8 Hz), 3.35 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 1.86 (m, 4H), 0.90 (t, 6H, J = 7.6 Hz) The following compound is basically as described in Example 135 and 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-Prepare using 5-thiazolyl]-2,6-dimethyl-imidazo [1,2-b] pyridazine and the specified amine.

Example 171

8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-1H-pyro-2-yl)-Preparation of imidazo [1,2-b] pyridazine

A solution of N-methylpyrrole (Aldrich, 800 µL, 9.0 mmol) in THF (10 mL) was cooled to -78 °C. under N₂ and then in tert-BuLi (pentane, 5.3 mL, 9.0 mmol) 1.7M). The solution is warmed to room temperature for 30 minutes, then cooled to -78 °C. and treated with ZnCl₂ (Aldrich, 0.5 M in THF, 18 mL, 9.0 mmol). The resulting mixture was warmed to room temperature and 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine (1.02 gm, 3.0 mmol). And PdCl₂(dppf) -CH₂Cl₂ complex (Aldrich, 149 mg, 0.17 mmol). The mixture is heated at 60 °C. overnight, then poured into saturated aqueous NH₄Cl (50 mL) and extracted with diethyl ether (75 mL). The organic extract is washed with water, brine, dried over Na₂SO₄, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) eluting the title compound (407.5 mg, 46% yield) as an oil. ES-MS (m / z): calcd (M + H)⁺: 297.5; analysis 297.5 (M + H)⁺: 297.5; ¹H NMR (400 MHz, CDCl₃): δ 6.86 (s, 1H), 6.65 (s, 1H), 6.52-6.28 (m, 2H), 3.50 (s, 3H), 3.35 (br s, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 1.87-1.75 (m, 4H), 0.87 (t, J = 7.0 Hz, 6H).

0.15 g, 0.24 mmol

Example 172

8-(1-ethyl-propyl)-2,6-dimethyl-3-[1-methyl-5-(3-methyl-thiophen-2-yl)-1H-pyrol-2-yl]-imidazo [1,2-b] pyridazine Preparation of [1,2-b] pyridazine

A. 3-(5-bromo-1-methyl-1H-pyro-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-1H-pyro-2-yl)-imidazo [1,2-b] pyridazine (474 mg, 1.40 mmol) The THF solution (10 mL) is cooled to 0 °C. and treated with NBS (250 mg, 1.40 mmol) in THF. Within 5 minutes, the reaction mixture is treated with saturated Na₂SO₃ (1 mL) and then concentrated. The resulting residue is diluted with ethyl acetate (50 mL) and washed with 50% aqueous saturated Na₂SO₃ (2 x 50 mL). The organic extract is dried over Na₂SO₄, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) eluting the title compound (374 mg, 71% yield) as a solid. ES-MS (m / z): calcd (M + H)⁺: 375; analysis 375 (M + H)⁺: 375; ¹H NMR (400 MHz, CDCl₃): δ 6.67 (s, 1H), 6.33 (d, J = 4.0 Hz, 1H), 6.30 (d, J = 4.0 Hz, 1H), 3.40 (s, 3H), 3.36 (br s, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H).

0.15 g, 0.24 mmol

B. 8-(1-ethyl-propyl)-2,6-dimethyl-3-[1-methyl-5-(3-methyl-thiophen-2-yl)-1H-pyrol-2-yl]-imidazo [1,2-b] pyridazine 3-(5-bromo-1-methyl-1H-pyrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (143 mg, 0.38 mmol) in THF slurry (5 mL) and PdCl₂(dppf) -CH₂Cl₂ complex (Aldrich, 19 mg, 0.023 mmol) was converted to 3-methyl-2-thienyl odor. Treat with zinc halide (Aldrich, 0.5 M in THF; 3.8 mL, 1.9 mmol) and then heat at 60 °C. for 1 h. The resulting mixture is poured into saturated NH₄Cl (25 mL) and extracted with diethyl ether (35 mL). The organic extract is washed with aqueous sodium chloride, dried over Na₂SO₄, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 15% ethyl acetate in hexane) to elute the product. The material is purified a second time by flash chromatography using a hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the product. As determined by MS analysis, only the fraction containing the pure required product is collected to yield the title compound (82.6 mg, 55% yield) as an oil. ES-MS (m / z): calcd (M + H)⁺: 392.2; analysis 393.1 (M + H)⁺: 393.1; ¹H NMR (400 MHz, CDCl₃): δ 7.28 (d, J = 5.3 Hz, 1H), 6.96 (d, J = 4.8 Hz, 1H), 6.67 (br s, 1H), 6.39 (d, J = 3.5 Hz, 1H), 6.37 (d, J = 4.0 Hz, 1H), 3.35 (br s, 1H), 3.33 (s, 3H), 2.52 (s, 3H), 2.51 (s, 3H), 2.26 (s, 3H), 1.89-1.76 (m, 4H), 0.87 (t, J = 7.5 Hz, 6H).

0.23 g, 0.38 mmol

Example 173

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-ylamine

50 mg of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.13 mmol) and 10 mg of copper (I) is added to 3 ml of 2M NH_3 in MeOH and the vial is covered with a cap tipped with Teflon wire and heated at 130 ° C. overnight. The reaction mixture is concentrated under N_2 gas and applied onto a silica gel chromatography column (hexane: AcOEt: 2M NH_3 is MeOH = 20: 20: 1) to yield 22 mg of the title compound. Yield 54%. Mass spectrum (m / e): 330 (M + 1); $^1\text{H-NMR}$ (CDCl_3): 6.72 (s, 1H), 5.24 (br, 2H), 3.40 (m, 1H), 2.56 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J = 7.4 Hz).

Example 174

N-[5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl]-morpholine

A. 7-bromo-3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine 547 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiazol-5-yl)-imidazo[1,2-b]pyridazine (1.74 mmol) and 341 mg NBS (1.92 mmol) is dissolved in 20 ml CH_2Cl_2 and stirred overnight at room temperature. The reaction mixture is washed with saturated $\text{Na}_2\text{S}_2\text{O}_5$, saturated NaCl, dried over Na_2SO_4 and evaporated. The crude material is applied onto a silica gel chromatography column (hexane: AcOEt = 8: 1) to yield 218 mg of the title compound. Yield 27%. Mass spectrum (m / e): 473 (M + 1); $^1\text{H-NMR}$ (CDCl_3): 3.44 (m, 1H), 2.70 (s, 3H), 2.45 (s, 3H), 2.37 (s, 3H), 2.03 (m, 4H), 0.90 (m, 6H).

B. N-[5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl]-morpholine 72 mg 7-bromo-3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.15 mmol) and 66 mg morpholine (0.76 mmol) and 97 mg cesium carboxylate (0.3 mmol) are placed in a 4 ml vial with 3 ml dry THF. The vial is covered with a cap lined with Teflon wire and heated at 100 ° C. overnight. The reaction mixture is concentrated and applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1) to produce 30 mg of the title compound. Yield 42%. Mass spectrum (m / e): 479 (M + 1); $^1\text{H-NMR}$ (CDCl_3): 3.87 (t, 4H, J = 5.0 Hz), 3.55 (t, 4H, J = 5.0 Hz), 3.45 (m, 1H), 2.70 (s, 3H), 2.44 (s, 3H), 2.40 (m, 2H), 2.18 (s, 3H), 2.01 (m, 2H), 0.88 (t, 6H, J = 7.3 Hz).

Example 175

3-[3-Chloro-4-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (hydrochloride salt)

Reike <(R)> Zn (0.5 g / ml. solution in THF (1.9 mL, 1.45 mmol)) was added to 3-(4-Bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.39 g, 0.73 mmol). The slurry was heated at 65 ° C. for 1 hour, placed in a centrifuge for 5 minutes, and the resulting solution was added 2-bromo-6-methyl-pyridine (0.12 g, 0.73 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.018 g, 0.024 mmol). The reaction is heated at 65 ° C. overnight, diluted with ethyl acetate (20 mL) and washed with a solution of saturated NH_4Cl (15 mL). The organic layer is dried over MgSO_4 , filtered and concentrated. The residue is purified by silica gel chromatography using a hexane and ethyl acetate gradient. The resulting product is dissolved in dichloromethane (5 mL), treated with a 1M solution of HCl in EtOH (0.35 mL, 0.35 mmol) and concentrated. The residue is recrystallized from ethyl acetate to produce the title compound (0.033 g, 0.072 mmol, 11%) from hexane. $^1\text{H-NMR}$ (CDCl_3): 6.95 (t, J = 7.3 Hz, 6H), 1.73-2.02 (m, 4H), 2.68 (s, 3H), 81 (s, 3H), 3.21 (s, 3H), 3.88-3.95 (m, 1H), 7.25 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.33 (dd, J = 7.5, 7.1 Hz, 1H), 9.26 (s, 1H) ppm. LC / MS (m / z): calcd S (M + H) +. 424.2; ANALYSIS: 424.2.

Example 176

3-(3-Chloro-4-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (hydrochloride) Salt

Using a procedure analogous to Example 175, 3-(4-Bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.46 g, 0.97 mmol), Reike <(R)> Zn (0.5 g / ml. solution in THF, 2.5 mL, 1.94 mmol), 3-iodo-pyridine (0.61 mL, 0.61 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.035 g, 0.048 mmol) and EtOH (0.61 mL, 0.61 mmol), the title compound (0.076 g, 0.17 mmol, 18%). $^1\text{H-NMR}$ (CDCl_3): 6.95 (t, J = 7.0 Hz, 6H), 1.71-1.85 (m, 2H), 1.85-2.01 (m, 2H), 2.68 (s, 3H), 2.81 (s, 3H), 3.85-3.96 (m, 1H), 5.28 (s, 1H), 7.27 (bs, 1H), 8.09 (bs, 1H), 8.20 (bs, 1H), 8.70 (bs, 1H), 8.89 (bs, 1H), 9.18 (bs, 1H). LC / MS (m / z): calcd S (M + H) +. 411.1; ANALYSIS: 411.2.

Example 177

Of 3-(3-Chloro-4-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine Preparation

Using a procedure analogous to Example 175, 3-(4-Bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.25 g, 0.61 mmol), Reike <(R)> Zn (0.5 g / ml. solution in THF, 1.6 mL, 1.21 mmol), 2-bromo-thiazol (0.11 mL, 1.21 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.022 g, 0.030 mmol) yield the title compound (0.012 g, 0.29 mmol, 5.8%). $^1\text{H-NMR}$ (CDCl_3): 6.89 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.52 (s, 6H), 2.7-3.43 (m, 1H), 5.73 (s, 1H), 7.43 (d, J = 3.3 Hz, 1H), 7.94 (d, J = 3.3 Hz, 1H), 8.30 (s, 1H) ppm. LC / MS (m / z): calcd (M + H) +: 417.1; ANALYSIS: 417.2.

Example 178

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl]-N-methylacetamide

60 mg of N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl]-N-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol), was dissolved in CH_2Cl_2 in 3.0 mL, is added acetyl chloride 16 mg of (0.2 mmol). The vial is covered with a Teflon lined cap and shaken at room temperature for 2 hours. The reaction mixture is concentrated and applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1 and Hexane: AcOEt = 2: 1) to produce 33.8 mg of the title compound. Yield 50%; mass spectrum (m / e): 366 (M + 1); $^1\text{H-NMR}$ (CDCl_3): 7.83 (s, 1H), 3.79 (s, 3H), 3.47 (m, 1H), 2.54 (s, 3H), 2.47 (s, 3H), 2.46 (s, 3H), 2.31 (s, 3H), 1.86 (m, 4H), 0.91 (t, 6H, J = 7.4 Hz).

Example 179

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl]-N-methanesulfonyl-methylamine

60 mg of N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl]-N-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 mL of CH_2Cl_2 and 23 mg of methanesulfonyl chloride (0.2 mmol) are added. The vial is covered with a Teflon lined cap and shaken at room temperature for 2 hours. The reaction mixture is concentrated and applied to silica gel chromatography (hexane: AcOEt = 2: 1) to yield 53.8 mg of the title compound. Yield 75%. Mass spectrum (m / e): 422 (M + 1); $^1\text{H-NMR}$ (CDCl_3): 6.96 (s, 1H), 3.60 (s, 3H), 3.34 (m, 1H), 2.19 (s, 3H), 2.56 (s, 3H), 2.48 (s, 3H), 2.29 (s, 3H), 1.86 (m, 4H), 0.90 (t, 6H), J = 7.4 Hz).

Example 180

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl]-N-ethanesulfonyl-methylamine

The title compound was dissolved in 50 mg of N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl]-N-methylamine. Prepared by a procedure analogous to Example 178 using 2-yl]-N-methylamine (0.15 mmol), 51 mg triethylamine (0.5 mmol) and 39 mg ethanesulfonyl chloride (0.3 mmol), 48.9 mg, yield 75%; mass spectrum

(m / e): 436 (M + 1); ¹H-NMR (CDCl₃): 6.73 (s, 1H), 3.62 (s, 3H), 3.42 (s, 2H, J = 7.4 Hz), 3.35 (m, 1H), 2.55 (s, 3H), 2.48 (s, 3H), 2.28 (s, 3H), 1.85 (m, 4H), 1.46 (t, 3H, J = 7.4 Hz), 0.90 (t, 6H, J = 7.5 Hz).

Example 181

3-[2-(1,1-Dioxo-thiomorpholin-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

60 mg of N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-yl] Thiomorpholine (0.14 mmol) is dissolved in 3 ml of CH₂Cl₂ and 62 mg of mCPBA (0.36 mmol) is added. The reaction mixture is stirred at room temperature for 30 minutes. The reaction mixture is diluted with CH₂Cl₂ and washed with saturated NaHCO₃ and saturated NaCl. The separated organic layer is dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel

chromatography column (hexane: AcOEt: 2M NH₃ in MeOH = 10: 3: 1) to produce 20.3 mg of the title compound. Yield 33%; mass spectrum (m / e): 448 (M + 1). ¹H-NMR: 6.72 (s, 1H), 4.16 (t, J = 4.7 Hz, 4H), 3.35 (m, 1H), 3.23 (t, J = 5.2 Hz, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).

Example 182

3-[2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-Imidazo [1,2-b] pyridazine

A. 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-yl-hydrazine title The compound is prepared using hydrazine essentially as described in Example 135. MS analysis value (M + 1) 345.

B. 3-[2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine 28 mg 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-yl-hydrazine (0.08 mmol) and 80 mg 2,4-pentanedione (0.8 mmol) are dissolved in 1.0 ml AcOH and heated at 100 ° C. for 2 hours. The reaction mixture is concentrated and applied onto a silica gel chromatography column (hexane: AcOEt = 5: 1) to produce 23 mg of the title compound. Yield 70%; mass spectrum (m / e): 409 (M + 1). 6.72 (s, 1H), 6.03 (s, 1H), 3.36 (m, J = 7.1, 14.1 Hz, 1H), 2.75 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).

Example 183

3-(3-Chloro-4-pyridin-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (hydrochloride) Salt

3-(4-Bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.25 g, solution of 61 mmol), 4-pyridyl-boronic acid (0.820, 67 mmol, Na₂CO₃) (0.5 mL, solution and n-PrOH of 2M of 0.91 mmol) of (2.5 mL), nitrogen Degas for 10 minutes. Pd(OAc)₂ (0.6027 g, 0.012 mmol) and PPh₃ (0.0095 g, 0.036 mmol) are added and the solution is heated at 90 ° C. overnight. The solution is diluted with ethyl acetate (40 mL) and washed with a solution of 10% Na₂CO₃ (30 mL). The organic layer is dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO flash chromatography (20% to 30% EtOAc gradient). The resulting product is dissolved in dichloromethane (5 mL), treated with a 1M solution of HCl in EtOH (0.35 mL, 0.35 mmol) and concentrated. The residue is recrystallized from acetonitrile and ethyl acetate to yield the title compound (0.15 g, 0.34 mmol, 56%). ¹H-NMR (CDCl₃): 5.095 (t, J = 7.5 Hz, 6H), 1.73-1.88 (m, 2H), 1.89-2.04 (m, 2H), 2.68 (s, 3H), 2.82 (s, 3H), 3.87-3.97 (m, 1H), 7.28 (s, 1H), 8.26-8.34 (m, 3H), 8.95 (d, J = 5.3 Hz, 2H) ppm. LC / MS (m / z): calcd S (M + H) +: 411.1; ANALYSIS: 411.2.

Example 184

3-[2-(3,6-Dihydro-2H-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-Imidazo [1,2-b] pyridazine

A. 4-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-yl]-Tetrahydro-pyran-4-ol 370 mg 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.93 mmol) dissolved in 10 ml dry THF, cooled to -78 ° C. and 0.6 ml n-BuLi 2.0M in hexane (1.2 mmol) was added. Stirred at -78 ° C for 30 minutes. Add 141 mg tetrahydro-6H-pyran-4-one (1.41 mmol) and stir at -78 ° C. for 2 h. The reaction mixture is diluted with AcOEt, washed with saturated NH₄Cl, dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel chromatography column (hexane: AcOEt: 2M NH₃ in MeOH = 10: 3: 1) to produce 152 mg of the title compound. Yield 40%. Mass spectrum (m / e): 415 (M + 1). ¹H NMR (CDCl₃): 6.74 (s, 1H), 3.99 (t, J = 2.2 Hz, 4H), 3.97 (t, J = 2.2 Hz, 4H), 3.35 (m, 1H), 3.20 (s, 3H), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 1.88 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).

B. 3-[2-(3,6-Dihydro-2H-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-Imidazo [1,2-b] pyridazine 150 mg of 4-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-yl]-tetrahydro-pyran-4-ol (0.36 mmol) was dissolved in 5 ml of CH₂Cl₂, 112 mg of triethylsilane (0.96 mmol) and 717 mg of tri Fluoroacetic acid (6.3 mmol) is added. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture is stirred at reflux for 1 hour and cooled to room temperature. Remove the solvent in vacuo. The crude product is applied onto a silica gel chromatography column (hexane: AcOEt: 2M NH₃ in MeOH = 10: 3: 1) to yield 64 mg of the title compound. Yield 45%. Mass spectrum (m / e): 397 (M + 1). 6.94 (s, 1H), 6.71 (s, 1H), 4.41 (d, J = 2.6 Hz, 2H), 3.96 (t, J = 5.3 Hz, 2H), 3.43 (m, 1H), 2.62 (s, 3H), 2.75 (m, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 1.86 (m, 4H), 0.92 (t, J = 8.2 Hz, 6H).

Example 185

8-(1-Ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(tetrahydro-pyran-4-yl)-thiazol-5-yl]-imidazo [1,2-b] Preparation of pyridazine

3-[2-(3,6-Dihydro-2H-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-Imidazo [1,2-b] pyridazine (55 mg, 0.14 mmol) 5% palladium on carbon (55 mg) and anhydrous ethanol (50 ml) are added to a pressure vessel. Remove the reactor with nitrogen, remove the reactor with hydrogen, pressurize the reaction mixture with hydrogen (415 KPa), seal the vessel, shake the reaction and heat at 40 ° C. The reaction is continued for 18 hours, heating is stopped and the reaction mixture is cooled to ambient temperature. Excess hydrogen is evacuated from the vessel and the vessel with nitrogen is removed. The reaction mixture is filtered to remove 5% palladium on carbon. The filtrate is concentrated and applied onto a silica gel chromatography column (hexane: AcOEt: 2M NH₃ in MeOH = 10: 3: 1) to produce 12.8 mg of the title compound. Yield 23%. Mass spectrum (m / e): 399 (M + 1). ¹H NMR (CDCl₃): 6.673 (s, 1H), 4.14 (m, 2H), 3.60 (m, 2H), 3.34 (m, 2H), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 2.16 (m, 2H), 2.02 (m, 2H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Example 186

Preparation of 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,6-dimethyl-8-(1-propyl-butyl)-imidazo [1,2-b] pyridazine

A. 6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine. 6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine was prepared according to J. Am. Heterocyclic Chem. Made using the chemistry described in 1991, 28, 583. A 250 mL 3-neck round bottom flask is filled with 3-amino-6-methylpyridazine (2.5 g, 0.0229 moles, 1.0 equiv), water (70 mL) and acetonitrile (50 mL). Concentrated sulfuric acid (3.51 g, 1.91 mL, 0.0344 moles, 1.5 eq), silver nitrate (3.87 g, 0.0229 moles, 1.0 eq) and valproic acid (7.21 g, 7.95 mL, 0.8 eq), 0.50 moles, 2.2 eq) is added to the reaction mixture. The reaction is heated to 75 ° C. As the reaction mixture was heated, a solution of (NH₄)₂S₂O₈ (7.85 g, 0.0344 mol, 1.5 eq) in 40 mL of water was slowly added via an addition funnel over 30 minutes. The reaction mixture is heated at 70-80 ° C. for a further 2 hours. The reaction mixture is cooled and dichloromethane is added. The reaction is basified with 30% aqueous soda solution and filtered through a short Celite® plug. The organic layer is separated and the aqueous layer is extracted twice more with dichloromethane. The combined organic extract is dried over Na₂SO₄. The solvent is evaporated and the crude material is purified using silica gel chromatography with a 2.0N solution of NH₃ in MeOH and dichloromethane as eluent. Yield = 0.61 g (13%) MS (APCI): 208 (M + 1)

B. 2,6-Dimethyl-8-(1-propyl-butyl)-imidazo [1,2-b] pyridazine. A 250 mL round bottom flask was charged with 6-methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine (0.611 g, 0.00295 moles, 1 eq), ethanol 2B (30 mL) and chloroacetone (0.382 g, 0.328 mL, 0.00412 moles, 1.4 equivalents). The reaction mixture is heated at 75 ° C. overnight and

then cooled to room temperature. NaHCO_3 (0.371 g, 0.00442 moles, 1.5 eq) is slowly added to the mixed reaction and heated at 100°C overnight. The reaction mixture is cooled and the solvent is evaporated. Dichloromethane is added and the reaction mixture is passed through filter paper. The solvent evaporates to produce a red oil that is purified via silica gel chromatography. The material is eluted with a hexane and ethyl acetate gradient to produce 0.511 g of final product. Check 2 peaks at $10/\text{ms}$. The mixture is used as "as is" in the next reaction. MS (APCI): 246 (M + 1).

C-3-Iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-b]pyridazine

A 50 mL round bottom flask is filled with 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-b]pyridazine (0.51 g, 0.0021 moles) and acetonitrile (3 mL). Place the reaction mixture in an ice bath and add stock NIS (0.468 g, 0.00208 moles). The reaction is stirred overnight to dissolve the ice bath. The next day, the reaction mixture is partitioned between a saturated aqueous solution of dichloromethane and NaHCO_3 . The organic layer is collected and the aqueous layer is extracted twice more with dichloromethane. Combine the organic extracts, wash with brine, and dry over Na_2SO_4 . The solvent is evaporated and the crude material is purified by silica gel chromatography eluting with hexanes to a 25:75 mixture of ethyl acetate and hexanes. Yield = 0.435 g (56%) MS (APCI): 372 (M + 1)

D-3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-b]pyridazine. A 15 mL round bottom flask was added to 3-iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-b]pyridazine (0.290 g, 0.000539 moles), 4-(4-Chloro-thiazol-2-yl)-morpholine (0.165 g, 0.000808 moles), Cs_2CO_3 (0.361 g, 0.00108 moles, 2.0 equivalents), $\text{Pd}(\text{DBA})_2$ (Fill with 0.0092 g, 0.000161 moles, 0.03 eq), PFPh_3 (0.00847 gram, 0.000323 moles, 0.060 eq) and DMF (2.0 mL). Nitrogen is bubbled through the reaction mixture for 15 minutes and then the reaction mixture is heated at 130°C overnight. The next day, the reaction mixture is divided into a saturated solution of Et_2O and NH_4Cl . The aqueous layer is extracted twice more with Et_2O . Combine the organic extracts and wash 2-3 times with H_2O , once with brine and dry over Na_2SO_4 . The solvent is evaporated in vacuo and the crude reaction mixture is purified via silica gel chromatography. Yield = 0.1737 g (72%) $^1\text{H-NMR}$ (CDCl_3): δ 9.87 (t, J = 7 Hz, 6H), 1.34-1.37 (m, 4H), 1.74 (t, J = 8 Hz, 4H), 2.54 (s, 3H), 2.59 (s, 3H), 3.48 (m, 1H), 3.53 (t, J = 5 Hz, 4H), 3.83 (t, J = 5 Hz, 4H), 5.71 (br s, 1H) ppm. LC / MS (m/z): Calculated $\text{C}_{22}\text{H}_{30}\text{ClN}_5\text{OS}$ (M + H) $^+$ = 448; Analytical value: 448.

Example 187

1-{5-[8-(1-Ethylpropyl)-2,6-dimethylimidazo[1,2-b]pyridazin-3-yl]-4-methylthiazol-2-yl}-Preparation of piperidin-4-one

A 8-{5-[8-(1-Ethylpropyl)-2,6-dimethylimidazo[1,2-b]pyridazin-3-yl]-4-methylthiazol-2-yl}-1,4-dioxo-6-aza-spiro[4.5]decane 100 mg of 3-(2-bromo-4-methylthiazol-5-yl)-8-(1-Ethylpropyl)-2,6-dimethylimidazo[1,2-b]pyridazine (0.25 mmol), 182 mg of 4-piperidine ethylene ketal (1.27 mmol) and 244 mg of Cs_2CO_3 (0.75 mmol).

Place in a 4.0 mL vial with 0 mL THF. The vial is covered with a cap lined with Teflon wire and heated at 110°C for 3 days. The reaction mixture is concentrated and applied onto a silica gel chromatography column (hexane: AcOEt = 3:1) to produce 116 mg of the title compound. Yield 100%. Mass spectrum (m/e): 456 (M + 1). $^1\text{H-NMR}$ (CDCl_3): δ 6.69 (s, 1H), 4.05 (s, 4H), 3.70 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.90-1.78 (m, 8H), 0.90 (t, J = 7.2 Hz, 6H).

B-1-{5-[8-(1-Ethylpropyl)-2,6-dimethylimidazo[1,2-b]pyridazin-3-yl]-4-methylthiazol-2-yl}-Piperidin-4-one 70 mg of 8-{5-[8-(1-Ethylpropyl)-2,6-dimethylimidazo[1,2-b]pyridazin-3-yl]-4-methylthiazol-2-yl}-1,4-dioxo-6-aza-spiro[4.5]decane (0.15 mmol). Dissolve in mL concentrated hydrochloric acid and stir at room temperature for 2 hours. The reaction mixture is neutralized with saturated NaHCO_3 , extracted with CH_2Cl_2 , dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica gel chromatography column (hexane: AcOEt = 2:1) to yield 33.2 mg of the title compound. Yield 52%. Mass spectrum (m/e): 412 (M + 1). $^1\text{H-NMR}$ (CDCl_3): δ 6.70 (s, 1H), 3.94 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.67 (t, J = 6.5 Hz, 4H), 2.57 (s, 3H), 2.47 (s, 3H), 2.21 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).

Example 188

{5-[8-(1-Ethylpropyl)-2,6-dimethylimidazo[1,2-b]pyridazin-3-yl]-4-methylthiazol-2-yl}-methyl Preparation of -amino- acetaldehyde

85 mg of N-{5-[8-(1-Ethylpropyl)-2,6-dimethylimidazo[1,2-b]pyridazin-3-yl]-4-methylthiazol-2-yl}-N-[[1,3]dioxolan-2-ylmethylmethylamine (0.2 mmol) is dissolved in 2 mL concentrated hydrochloric acid and stirred at 50°C for 30 minutes. The mixture is cooled to room temperature and washed with saturated NaHCO_3 . The mixture is extracted with CH_2Cl_2 , dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica gel chromatography column (CH_2Cl_2 : MeOH = 20:1) to yield 73.4 mg of the title compound. Yield 76%. Mass spectrum (m/e): 386 (M + 1). 9.79 (s, 1H), 6.72 (s, 1H), 4.39 (s, 2H), 3.36 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).

Example 189

4-{3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-2,6-dimethylimidazo[1,2-b]pyridazin-8-yl}-heptane-4-ol

A-3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-2,6-dimethylimidazo[1,2-b]pyridazine

2,6-Dimethylimidazo[1,2-b]pyridazine (0.32 g (2.17 mmol) solution) 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-1H-triazoles of [1,2,4]-le (0.72g, 2.61mmol), Cs_2CO_3 (1.49g, 4.37mmol) and DMF (6 mL), to 15 minutes degassing with H_2 . $\text{Pd}(\text{OAc})_2$ (0.024 g, 0.11 mmol) and PFPh_3 (0.057 g, 0.22 mmol) are added and the solution is heated at 135°C for 4 hours. The solution is diluted with CH_2Cl_2 (50 mL), washed with saturated NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) to yield the title compound (0.29 g, 0.84 mmol, 39%). $^1\text{H-NMR}$ (CDCl_3): δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). LC / MS (m/z): calcd (M + H) $^+$ = 345.1; ANALYSIS: 345.2.

B-1-{3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-2,6-dimethylimidazo[1,2-b]pyridazin-8-yl}-butan-1-one

3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-2,6-dimethylimidazo[1,2-b]pyridazine (0.20 g, 0.58 mmol), N-methoxy-N-methylbutylamide (Wolberg, M. et. Al. Chem. Europ. J. 2001, 7, 4562 in THF (3 mL), J) (0.084 g, 0.64 mmol) is cooled to -78°C and a 2.0 M solution of LDA in heptane / THF / ethylbenzene (0.58 mL, 1.16 mmol) is added. The solution is warmed to ambient temperature, diluted with dichloromethane (20 mL) and washed with saturated NH_4Cl solution (15 mL). The organic layer is dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-100% EtOAc gradient) to yield the title compound (0.11 g, 0.27 mmol, 46%). $^1\text{H-NMR}$ (CDCl_3): δ 1.04 (t, J = 7.0 Hz, 3H), 1.76-1.86 (m, 2H), 2.56 (s, 3H), 2.59 (s, 3H), 3.51 (t, J = 7.1 Hz, 2H), 4.15 (s, 3H), 7.36 (s, 1H), 7.49 (s, 1H), 7.90 (s, 1H) ppm. LC / MS (m/z): Calculated $\text{C}_{19}\text{H}_{21}\text{ClN}_6\text{OS}$ (M + H) $^+$ = 415.1; Analytical value: 415.3.

C-4-{3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-2,6-dimethylimidazo[1,2-b]pyridazin-8-yl}-heptane-4-ol 1-{3-[3-chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-2,6-dimethylimidazo[1,2-b]pyridazin-8-yl}-butan-1-one (0.15 g, 0.36 mmol) and THF (5 mL) is cooled to 0°C and a 2.0 M propylmagnesium bromide solution in diethyl ether (0.22 mL, 0.43 mmol) is added. The reaction is warmed to ambient temperature, diluted with ethyl acetate (30 mL) and washed with saturated NH_4Cl solution (30 mL). The organic layer is dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-40% EtOAc gradient) to yield the title compound (0.016 g, 0.017 mmol, 47%). $^1\text{H-NMR}$ (CDCl_3): δ 0.90 (t, J = 7.4 Hz, 6H), 1.12-1.29 (m, 2H), 1.37-1.54 (m, 2H), 1.86-2.04 (m, 4H), 2.50 (s, 3H), 2.54 (s, 3H), 4.15 (s, 3H), 5.71 (br s, 1H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H) ppm. LC / MS (m/z): calcd (M + H) $^+$ = 459.2; ANALYSIS: 459.3.

Examples 190, 191 and 192

7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine, 3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine, 3-(4-bromo-thiazol-4-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine

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191

192

A. 8-(1-ethyl-propyl)-2,6-dimethyl-5-thiazol-5-yl-imidazo [1,2-b] pyridazine 2.41 g (7 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine, 3.00 g thiazol (35.2 mmol), 378 mg triphenylphosphine (1.44 mmol) and 4.71 g of Cs_2CO_3 (14.5 mmol) is mixed with 25 ml of DMF and N_2 gas is bubbled for 30 minutes. 330 mg of Pd_2dba_3 (0.36 mmol) is added and the tube is sealed. The reaction tube is heated at 130 °C overnight. To the reaction mixture is added water and CH_2Cl_2 and the CH_2Cl_2 layer is separated, washed with saturated NaCl and dried over Na_2SO_4 . The solvent is removed in vacuo and the crude product is applied onto a silica gel chromatography column (hexane: AcOEt = 3:1) to yield 1.48 mg of the title compound. Yield 70%. Mass spectrum (m/e): 301 (M+1); $^1\text{H-NMR}$ (CDCl_3): 8.93 (s, 1H), 8.52 (s, 1H), 6.78 (s, 1H), 3.35 (m, 1H), 2.76 (s, 3H), 2.66 (s, 3H), 1.86 (m, 4H), 0.89 (t, 6H, J = 7.5 Hz).

B. 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine; (2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine 8-(1-ethyl-propyl)-2,6-dimethyl 1.05 g (3.5 mmol) of 3-thiazol-5-yl-imidazo [1,2-b] pyridazine and 1.56 g NBS (8.75 mmol) dissolved in 50 ml CH_2Cl_2 and stir at room temperature for 3 days. The reaction mixture is diluted with CH_2Cl_2 and washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$. The separated organic layer is dried over Na_2SO_4 and evaporated. The reaction mixture was applied onto a silica gel chromatography column (hexane: AcOEt = 20:1 to 8:1) to give 3 products, 149 mg of 7-bromo-3-(2,4-dibromo)-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (9%), 936 mg of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (58%), 77 mg of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (6%) is obtained. 7-Bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine mass spectrum (m/e): 508 (M+1); $^1\text{H-NMR}$ (CDCl_3): 3.45 (m, 1H), 2.71 (s, 3H), 2.52 (s, 3H), 2.38 (m, 2H), 2.02 (m, 2H), 0.68 (t, 6H, J = 7.5 Hz); 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine mass spectrum (m/e): 459 (M+1); $^1\text{H-NMR}$ (CDCl_3): 6.79 (s, 1H), 5.33 (m, 1H), 2.57 (s, 3H), 2.55 (s, 3H), 1.87 (m, 4H), 0.90 (t, 6H, J = 7.5 Hz); 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine mass spectrum (m/e): 380 (M+1); $^1\text{H-NMR}$ (CDCl_3): 9.01 (s, 1H), 6.77 (s, 1H), 3.35 (m, 1H), 2.55 (s, 3H), 2.54 (s, 3H), 1.87 (m, 4H), 0.91 (t, 6H, J = 7.5 Hz).

Example 193

Preparation of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

100 mg (0.22 mmol) of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.22 mmol), 96 mg morpholine (1.1 mmol) and 215 mg Cs_2CO_3 (0.66 mmol) are placed in a 4 ml vial with dry THF and the vial is covered with a Teflon cap. The vial is heated at 120 °C overnight. The reaction mixture is applied onto a silica gel chromatography column (hexane: AcOEt: 3M NH_3 in MeOH = 9:3:1) to yield 72.2 mg of the title compound. Yield 71%. Mass spectrum (m/e): 465 (M+1); $^1\text{H-NMR}$ (CDCl_3): 6.73 (s, 1H), 3.87 (t, 4H, J = 5.1 Hz), 3.58 (t, 4H, J = 5.1 Hz), 3.35 (m, 1H), 2.57 (s, 3H), 2.53 (s, 3H), 1.86 (m, 4H), 0.90 (t, 6H, J = 7.5 Hz).

The following compounds are prepared essentially as described in Example 193. Examples 194-197 are examples of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine. (0.22 mmol) is used and is called an amine. Example 198 contains 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] Pyridazine is used and is called amine.

Examples 199 and 200

N-(4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl)-Of morpholine and N-(5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl)-morpholine Preparation:

199

200

Method A

40 mg of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine and 25 mg of CuCl (0.25 mmol) are placed in a 4 ml vial with 2 ml of dry DMF and covered with a Teflon cap. The vial is heated at 120 °C overnight. The reaction mixture is filtered, washed with CH_2Cl_2 and the filtrate is concentrated. The crude product mixture was applied onto a silica gel chromatography column (hexane: AcOEt = 2:1 and Hexane: AcOEt = 8:1) to give two products, 4.2 mg of N-(4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl)-morpholine (12%), 7.2 mg N-(5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl)-Morpholine (22%) is obtained. N-(4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl)-Morpholine mass spectrum (m/e): 420 (M+1); $^1\text{H-NMR}$ (CDCl_3): 6.73 (s, 1H), 3.88 (t, 4H, J = 5.0 Hz), 3.57 (t, 4H, J = 5.0 Hz), 3.35 (m, 1H), 2.57 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J = 7.5 Hz). N-(5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl)-morpholine mass spectrum (m/e): 396 (M+1); $^1\text{H-NMR}$ (CDCl_3): 7.75 (s, 1H), 6.70 (s, 1H), 3.91 (t, 4H, J = 5.0 Hz), 3.51 (t, 4H, J = 5.0 Hz), 3.34 (m, 1H), 2.67 (s, 3H), 2.61 (s, 3H), 1.85 (m, 4H), 0.88 (t, 6H, J = 7.5 Hz).

Method B

N-(4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl)-Morpholine A 20 L reactor flask under nitrogen is filled with 2900 ml of dry and degassed DMF and then 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine (287 g, 0.836 mol), 2-mol phorino-4-chlorothiazol (205.4 g, 1.67 mol, 1.2 equiv), $\text{Pd}(\text{OAc})_2$ (3.74 g, 7.91 mmol, 0.01 eq), triphenylphosphine (6.77 g, 33.1 mmol, 0.04 eq), copper iodide (8 g, 41.59 mmol, 0.05 eq) and cesium carboxylate (544.9g, 1.65mol) filled with. The reaction mixture is heated at 120 °C. After 16 hours at 120 °C, 1.57 g $\text{Pd}(\text{OAc})_2$ and 4.38 g triphenylphosphine are added. After 1 hour, the mixture is cooled, quenched with NH_4Cl solution (4300 mL), extracted with MTBE (2900 mL), and the aqueous phase is extracted twice more with 2000 ml MTBE. The organic phase is washed with a saturated NaCl aqueous phase (2000 mL), then treated with 72 g of charcoal in a flask and filtered through Celite®. The filtrate is concentrated in vacuo to yield 373.8 g (79.3%) of the title compound, which is 81.4 area% by HPLC analysis, the remainder is solvent, and no by-product was detectable in Example 200.

The following title compound is prepared essentially as described in Method A of Examples 199 and 200.

Example 207

N-(5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-yl)-morpholine Preparation of -yl)-morpholine

50 mg of N-(5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-yl)-morpholine (0.1 mmol) is dissolved in 2.0 ml dry DMF and 31 mg CuCl (0.3 mmol) is added. The vial is covered with a cap lined with Teflon wire and heated at 120 °C overnight. The reaction mixture is applied onto a silica gel chromatography column (hexane: AcOEt = 3:1) to produce 39.2 mg of the title compound. Yield 87%. Mass spectrum (m/e): 435 (M+1), 3.33 (t, J = 4.8 Hz, 4H), 3.57 (t, J = 5.1 Hz, 4H), 2.64 (s, 3H), 2.44 (s, 3H), 2.18 (s, 3H), 2.00 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 208

N-[5-[7-bromo-8-(1-ethyl-propyl)-2,6,7-trimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl]-morpholine
50 mg N-[5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl]-morpholine (0.1 mmol) is dissolved in 4 ml Et₂O and cooled to -78 °C. Add 0.09 ml of n-BuLi 1.6 M in hexane (0.15 mmol) at -78 °C and stir at -78 °C for 20 minutes. 43 mg iodomethane (0.3 mmol) is added to the mixture, stirred at -78 °C, and allowed to come to room temperature overnight. The reaction was quenched with saturated NH₄Cl and Et₂O. Extract with The separated organic layer is dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1) to yield 29.6 mg of the title compound. Yield 69%. Mass spectrum (m / e): 414 (M + 1). ¹H NMR (CDCl₃): δ 3.87 (t, J = 4.6 Hz, 4H), 3.56 (t, J = 4.6 Hz, 4H), 3.35 (m, 1H), 2.54 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 2.01 (m, 4H), 0.88 (m, 6H).

Example 209

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl]-Morpholine preparation
170 mg of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.37 mmol) and 100 mg sodium trifluoroacetate (0.74 mmol) are dissolved in 3 ml DMF / toluene = 2/1. N₂ gas is bubbled through the mixture for 20 minutes and 141 mg of CuI (0.74 mmol) is added. The vial is sealed and heated in the microwave at 210 °C for 30 minutes. The reaction mixture is applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1 and CH₃CN: CH₂Cl₂ : Hexane = 5: 45: 50) to produce 64.3 mg of the title compound. Yield 38%. Mass spectrum (m / e): 454 (M + 1). ¹H NMR (CDCl₃): δ 6.72 (s, 1H), 3.88 (m, 4H), 3.60 (m, 4H), 3.32 (m, 1H), 2.54 (s, 3H), 2.47 (s, 3H), 1.85 (m, 4H), 0.89 (t, J = 7.0 Hz, 6H).

Example 210

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-phenyl-thiazol-2-yl]-Preparation of morpholine
50 mg of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.11 mmol), 40 mg phenylboronic acid (0.33 mmol) and 0.27 ml of 2M Na₂CO₃ eq. (0.55 mmol) is added to 2.5 ml DME / water / EtOH = 7/3/1. N₂ gas is bubbled through the mixture for 20 minutes and 20 mg of Pd(PPh₃)₄ (0.017 mmol) is added. The vial is sealed and heated in the microwave at 160 °C for 30 minutes. The reaction mixture is added to CH₂Cl₂ and water, the organic layer is separated, washed with brine, dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel chromatography column (hexane: AcOEt = 10: 1) to produce 27 mg of the title compound. Yield 54%. Mass spectrum (m / e): 462 (M + 1). δ 8.29 (m, 1H), 7.60 (m, 2H), 7.44 (m, 1H), 7.22 (m, 1H), 6.70 (s, 1H), 3.90 (t, J = 4.6 Hz, 4H), 3.64 (t, J = 5.0 Hz, 4H), 3.36 (m, 1H), 2.52 (s, 3H), 2.09 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 211

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methoxy-thiazol-2-yl]-Preparation of morpholine
100 mg of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.22 mmol), 24 mg sodium methoxide (0.44 mmol) and 21 mg CuI (0.11 mmol) are placed in a 4 ml vial with 3 ml MeOH and capped with a Teflon lined cap. The reaction vial is heated at 130 °C overnight. The reaction mixture is concentrated and applied onto a silica gel chromatography column (hexane: THF = 10: 1) to produce 32.8 mg of the title compound. Yield 36%. Mass spectrum (m / e): 416 (M + 1). ¹H NMR (CDCl₃): δ 6.64 (s, 1H), 3.96 (s, 3H), 3.86 (t, J = 4.7 Hz, 4H), 3.53 (m, 4H), 3.34 (m, 1H), 2.82 (s, 3H), 2.48 (s, 3H), 1.82 (m, 4H), 0.85 (t, J = 7.4 Hz, 6H).

Example 212

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-fluoro-thiazol-2-yl]-Preparation of morpholine
50 mg of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.11 mmol) was dissolved in 4 ml of diethyl ether, cooled to -78 °C, and 0.1 ml of n-BuLi 1.6 M in hexane (0.16 mmol) was added at -78 °C. And stir at -78 °C for 20 minutes. 104 mg N-fluorobenzenesulfonimide (0.33 mmol) in 2 ml toluene was added at -78 °C, stirred for 1 hour at room temperature, saturated NH₄Cl was added, the mixture was extracted with Et₂O, Na Dry over Na₂SO₄ and evaporate. The crude product is applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1) to yield 4.1 mg of the title compound. Yield 10%. Mass spectrum (m / e): 404 (M + 1). 6.71 (s, 1H), 3.87 (t, J = 4.6 Hz, 4H), 3.55 (t, J = 5.0 Hz, 4H), 3.34 (m, 1H), 2.56 (s, 3H), 2.54 (s, 3H), 1.84 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 213

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-iodo-thiazol-2-yl]-Preparation of morpholine
50 mg of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.11 mmol), 30 mg CF₃CO₂Na (0.22 mmol) and 42 mg CuI (0.22 mmol) are placed in a 4 ml vial with DMF / toluene = 2: 1. The vial is covered with a Teflon cap and heated at 150 °C overnight. The reaction mixture is applied onto a silica gel chromatography column (hexane: AcOEt = 5: 1) to produce 54 mg of the title compound. 96%. Mass spectrum (m / e): 512 (M + 1). ¹H NMR (CDCl₃): δ 6.71 (s, 1H), 3.87 (t, J = 5.4 Hz, 4H), 3.58 (t, J = 5.4 Hz, 4H), 3.36 (m, 1H), 2.57 (s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 5.4 Hz, 6H).

Example 214

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-2-morpholin-4-yl-thiazol-4-carbonitrile Preparation
50 mg of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.11 mmol) and 30 mg CuCN (0.33 mmol) are placed in a 4 ml vial with 2 ml DMF and the vial is covered with a Teflon cap. The vial is heated at 150 °C overnight. The reaction mixture is applied onto a silica gel chromatography column (hexane: AcOEt = 5: 1) to produce 12.3 mg of the title compound. Yield 28%. Mass spectrum (m / e): 411 (M + 1). 6.77 (s, 1H), 3.89 (t, J = 4.8 Hz, 4H), 3.61 (t, J = 5.0 Hz, 4H), 3.32 (m, 1H), 2.62 (s, 3H), 2.59 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 215

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-iodo-thiazol-2-yl] Preparation of N-isopropyl-methylamine
The title compound is prepared essentially as described in Example 213 as N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine-3-yl]-4-bromo-thiazol-2-yl]-N-isopropyl-methylamine to yield 17.9 mg. Yield 22%; mass spectrum (m / e): 496 (M + 1). ¹H NMR (CDCl₃): δ 6.71 (s, 1H), 4.41 (m, 1H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.53 (s, 3H), 1.84 (m, 4H), 1.29 (d, J = 5.8 Hz, 6H), 0.90 (t, J = 7.2 Hz, 6H).

Example 216

N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methoxy-thiazol-2-yl]-Preparation of N-isopropyl-methylamine
The title compound was prepared essentially as described in Example 211 by N-[5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine-3-yl]-4-bromo-thiazol-2-yl]-N-isopropyl-methylamine to yield 52.7. Yield 36%. Mass spectrum (m / e): 402 (M + 1). ¹H NMR (CDCl₃): δ 6.63 (s, 1H), 4.44 (m, 1H), 3.96 (s, 3H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.50 (s, 3H), 1.83 (m, 4H), 2.9 (d, J = 6.7 Hz, 6H), 0.88 (t, J = 5 Hz, 6H).

Examples 217 and 218

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-carboxylic acid amide and 5-Preparation of [8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-carboxylic acid N-methylamide

217

218

180 mg 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.46 mmol) and 124 mg of copper (I) cyanide into a 4 ml vial with 2 ml of dry DMF. The vial is closed with a Teflon cap and heated at 130 ° C. overnight. The crude reaction mixture was applied onto a silica gel chromatography column (hexane: AcOEt = 1: 1 to 1: 3) and 52.1 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-carboxylic acid (32%), 7.6 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-carboxylic acid methylamide is produced.

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-carboxylic acid amide, mass spectrum (M / e): 358 (M + 1). ¹ H NMR (CDCl₃): δ 7.21 (s, NH), 6.76 (s, 1H), 5.59 (s, 1H), 3.34 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.42 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H). And 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-carboxylic acid methylamide, and Mass spectrum (m / e): 372 (M + 1). ¹ H NMR (CDCl₃): 8.77 (s, NH), 6.75 (s, 1H), 4.06 (s, 3H), 3.35 (m, 1H), 2.55 (s, 3H), 2.49 (s, 3H), 2.43 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Example 219

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-carboxylic acid dimethylamide

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-carboxylic acid amide (46 mg, 0.13 mmol) and 28 mg sodium tert-butoxide (0.30 mmol) in 4 ml dry DMSO and stirred at room temperature for 5 min. Add 141 mg iodomethane (1.0 mmol) and stir at room temperature for 1 h. Water is added and the mixture is extracted with CH₂Cl₂, dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1) to produce 22.3 mg of the title compound. Yield 45%; mass spectrum (m / e): 386 (M + 1). 6.75 (s, 1H), 3.70 (s, 3H), 3.35 (m, 1H), 3.21 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.41 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).

Example 220

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo [1,2-b] pyridazine

A solution of 3-methylfuran (Acros, 232 mg, 2.83 mmol) in THF (5 mL) was cooled to -78 ° C. under N₂ and then nBuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol). After the addition of nBuLi, the solution is warmed to 0 ° C. for 15 minutes and then warmed to room temperature for an additional 5 minutes. The reaction mixture is then cooled to -78 ° C. and treated with ZnCl₂ (Aldrich, 0.5 M in THF, 5.8 mL, 2.9 mmol). The resulting mixture was warmed to room temperature and 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine (400 mg, 1.17 mmol) and PdCl₂(dppf)·CH₂Cl₂ complex (Aldrich, 95 mg, 0.12 mmol). The mixture is heated at 60 ° C. for 4 hours, then 1N HCl (60 mL) is injected and extracted with ethyl acetate (2 x 50 mL). The combined organic extract is washed with water, brine, dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by chromatography using a hexane-ethyl acetate gradient (20% ethyl acetate to 100% hexane in hexane) to give the title compound as an oil pyridazine (149 mg, 43% yield). Elute. ES-MS (m / z): Calculated value C₁₈H₂₃N₃O: 297.2; Anal. Value 298.5 (M + H); ¹ H NMR (400 MHz, CDCl₃): δ 7.59 (d, J = 1.8 Hz, 1H), 6.71 (s, 1H), 6.47 (d, J = 1.8 Hz, 1H), 3.36 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.10 (s, 3H), 1.92-1.79 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).

Example 221

Preparation of 3-(5-bromo-3-methyl-furan-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo [1,2-b] pyridazine (32.4 mg, 0.11 mmol) in CH₂Cl₂ solution (4 mL) is cooled to 0 ° C. under a CaSO₄ drying tube and treated with NBS (20.1 mg, 0.11 mmol). After 15 minutes at 0 ° C., the mixture is warmed to room temperature. After an additional 10 minutes, the reaction mixture is poured into H₂O (25 mL) and extracted with CH₂Cl₂ (2 x 25 mL). The combined organic extract is washed with water, brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by chromatography using a hexane-ethyl acetate gradient (10% ethyl acetate to 100% hexane in hexane) to give the title compound (26.3 mg, 64% yield) as a solid. ES-MS (m / z): Calculated value C₁₈H₂₂BrN₃O: 375.1; Anal. 376.2 (M + H); ¹ H NMR (400 MHz, CDCl₃): δ 6.72 (s, 1H), 6.40 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.49 (s, 3H), 2.07 (s, 3H), 93-1.77 (m, 4H), 0.89 (t, J = 7.5 Hz, 6H).

Example 222

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo [1,2-b] pyridazine

A. A solution of 2,3-dibromofuran (Lancaster, 5.54 gm, 24.5 mmol) in THF (10 mL) under 3-bromo-2-methylfuran N₂ was added to PdCl₂(PPh₃)₂ (860 mg, 1.2 mmol) and stirred at room temperature for 10 minutes. The solution is then treated with CH₃ZnCl (Aldrich, 2.0 M in THF, 15 mL, 30 mmol). The resulting mixture is stirred overnight at room temperature, then poured into 1N HCl and extracted with diethyl ether. The organic extract is washed with saturated NaCl, dried over Na₂SO₄ and filtered. The filtrate is then distilled and the product is collected at 120-125 ° C. to yield the title compound as a colorless oil (1.71 gm, 43% yield). ¹ H NMR (400 MHz, CDCl₃): δ 7.25 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 2.28 (s, 3H).

B. 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo [1,2-b] pyridazine 3-bromo-2-methylfuran (above) (1.06 gm, 6.58 mmol) in THF (10 mL) was cooled to -78 ° C. under N₂ and then nBuLi (1.6 M in hexane, 4.1 mL, 6 mL), 6 mmol. After 10 minutes at -78 ° C., the mixture is treated with ZnCl₂ (Aldrich, 0.5 M in THF, 13.2 mL, 6.6 mmol). The resulting mixture was warmed to room temperature and then 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine (1.13 gm, 3.29 mmol) and PdCl₂(dppf)·CH₂Cl₂ complex (Aldrich, 257 mg, is treated with 0.31 mmol). The mixture is heated at 60 ° C. for 4 hours, then poured into saturated NH₄Cl (50 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic extracts are washed with saturated NaCl, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by chromatography using a hexane-ethyl acetate gradient (20% ethyl acetate to 100% hexane in hexane) to afford the title product (685 mg, 70% yield) as an oil. Elute. ES-MS (m / z): Calculated value C₁₈H₂₃N₃O: 297.2; Anal. Value 298.2 (M + H); ¹ H NMR (400 MHz, CDCl₃): δ 7.45 (d, J = 2.9 Hz, 1H), 6.63 (s, 1H), 6.60 (d, J = 2.0 Hz, 1H), 3.35-3.31 (m, 1H), 2.51 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H), 1.88-1.75 (m, 4H), 0.86 (t, J = 7.5 Hz, 6H).

Example 223

Preparation of 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo [1,2-b] pyridazine (42.3 mg, under a CaSO₄ drying tube 0.14 mmol) of a CH₂Cl₂ solution of the (2 mL), treated with N-bromosuccinimide (27.6 mg, 0.16 mmol). After 30 minutes, the reaction mixture is poured into H₂O (25 mL) to extract CH₂Cl₂ (2 x 25 mL). The combined organic extracts are washed with saturated NaCl, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by chromatography using a hexane-ethyl acetate gradient (12% ethyl acetate to 100% hexane in hexane) to yield the title product (36.9 mg, yield) as a white solid. 75%). ES-MS (m / z): calcd 375.1; analysis 376.3 (M + H); ¹ H NMR (400 MHz, CDCl₃): δ 6.67 (s, 1H), 6.50 (s, 1H), 3.33 (m, 1H), 2.53 (s, 3H), 2.44 (s, 3H), 2.29 (s, 3H), 90-1.73 (m, 4H), 0.86 (t, J = 7.3 Hz, 6H).

Example 224

Preparation of 3-(2,4-dimethyl-2H-pyrazol-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

nBuLi (1.3 mL, 2.99 mmol) is stirred with THF (4 mL) under N₂ and cooled to -72 ° C. 1,4-Dimethyl-1H-pyrazol (170 mg, 2.04 mmol in 1 mL THF) is added slowly and stirred

for 5 minutes, then warmed to room temperature and stirred for 45 minutes. The mixture is cooled to -72°C , and zinc chloride solution (4.3 mL, 2.14 mmol, 0.5 M in toluene) is added and warmed to ambient temperature. 8-(1-ethyl-propyl)-3-*tert*-butyl-2,6-dimethyl-imidazo [1,2-*b*] pyridazine and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ complex (Aldrich, 40 mg, 0.05 mmol). The mixture is heated at 65°C overnight, cooled to ambient temperature, added to water and extracted twice with EtOAc. The combined organic extract is washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (50% ethyl acetate to 100% hexane in hexane) to elute the product. The title compound is produced (0.7% yield). ES-MS (m/z): calcd $[\text{M} + \text{H}]^+$: 312.2; analysis 312.2 ($\text{M} + \text{H})^+$. ^1H NMR (400 MHz, CDCl_3): δ 7.51 (s, 1H), 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.53 (s, 3H), 2.43 (s, 3H), 2.00 (s, 3H), 1.87 (m, 4H), 0.92 (m, 6H).

Example 225

Of 3-(4,5-dibromo-2-methyl-2H-pyrazol-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-*b*] pyridazine Preparation

8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo [1,2-*b*] pyridazine (300 mg, 1.4 mmol), 3,4,5-tribromo-1-methyl-1H-pyrazole (700 mg, 2.1 mmol) and cesium carboxylate (900 mg, 2.8 mmol) are stirred with DMF (5 mL) and degassed by bubbling a stream of nitrogen through the mixture. $\text{PdCl}_2(\text{PPh}_3)_2$ (14 mg) is added and the mixture is heated at 130°C overnight. The mixture is added to water and extracted twice with EtOAc. The combined organic extract is washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (from 100% hexane to 20% ethyl acetate in hexane) to elute the title product (204 mg, 32% yield). ES-MS (m/z): calcd $[\text{M} + \text{H}]^+$: 455.2; analysis 455.9 ($\text{M} + \text{H})^+$. ^1H NMR (400 MHz, CDCl_3): δ 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.51 (s, 3H), 2.45 (s, 3H), 1.84 (m, 4H), 0.88 (t, 6H).

Example 226

8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl)-imidazo [1,2-*b*] Preparation of pyridazine / benzenesulfonic acid

8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl)-imidazo [1,2-*b*] To a solution of pyridazine (0.23 g, 0.57 mmol) and MeOH (1 mL) is added a solution of benzenesulfonic acid (0.096 g, 0.57 mmol) and MeOH (1 mL). Concentrate the solution to produce the title compound (0.32 g, 0.57 mmol, > 99%). ^1H NMR (CDCl_3): δ 0.79 (t, $J = 7.0$ Hz, 6H), 1.59-1.82 (m, 4H), 2.06 (s, 3H), 2.61 (s, 6H), 2.58 (s, 3H), 3.22-3.32 (m, 1H), 6.79 (bs, 2H), 7.25 (s, 1H), 7.33-7.42 (m, 3H), 7.49 (d, $J = 7.9$ Hz, 1H), 7.80 (d, $J = 7.4$ Hz, 2H), 7.92 (dd, $J = 7.4, 1.6$ Hz, 1H), 8.23 (s, 1H). LC / MS (m/z): calcd $[\text{M} + \text{H}]^+$: 405.2; ANALYSIS: 405.4.

Example 227

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-morpholin-4-yl-thiophen-2-yl)-imidazo [1,2-*b*] pyridazine

3-(4-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-*b*] pyridazine (0.30 g, 0.76 mmol), morpholine (0.10 mL, 1.15 mmol), $\text{Pd}_2(\text{dba})_3$ (0.035 g, 0.038 mmol) and 2-dicyclohexylphosphino-biphenyl-2'-[N,N-dimethyl-amino] 1M LiHMDS (1.9 mL, 1.91 mmol) is added to a flask containing biphenyl (0.018 g, 0.046 mmol). The solution is heated at 65°C overnight, diluted with EtOAc (30 mL), washed with water (20 mL), brine (20 mL), dried over MgSO_4 , filtered and concentrated. The residue is clarified with ISCO (15%-30% EtOAc gradient), dissolved in Et₂O (20 mL) and extracted with 1M HCl (2 x 30 mL). The aqueous layer was washed with Et₂O (20 mL), basified with 5M NaOH (15 mL), extracted with EtOAc (2 x 20 mL), the combined organic layers were washed with brine (40 mL), dried over MgSO_4 . Filter and concentrate to produce the title compound (0.047 g, 0.12 mmol, 16%). ^1H NMR (CDCl_3): δ 0.87 (t, $J = 7.5$ Hz, 6H), 1.73-1.91 (m, 4H), 2.01 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 2.99-3.05 (m, 4H), 3.28-3.37 (m, 1H), 3.84-3.88 (m, 4H), 6.65 (s, 1H), 6.71 (s, 1H). LC / MS (m/z): calcd $[\text{M} + \text{H}]^+$: 399.2; ANALYSIS: 399.2.

Example 228

8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-furan-3-yl)-imidazo [1,2-*b*] pyridazine Preparation

A solution of 2-bromothiazol (Aldrich, freshly sterilized, 75.0 μL , 0.84 mmol) in THF (5 mL) was cooled to -78°C under N_2 and then n-BuLi (1.6M, 0.52 mL, 0.83 mmol). After 15 minutes at -78°C , the mixture is treated with ZnCl_2 (Aldrich, 0.5 M in THF, 1.8 mL, 0.90 mmol). The resulting mixture was warmed to room temperature and then 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-*b*] pyridazine (60.1 mg, 0.16 mmol) and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ complex (Aldrich, 22 mg, 0.027 mmol) is treated with THF slurry (1 mL) containing. The mixture is heated at 60°C overnight, then poured into saturated NH_4Cl and extracted with diethyl ether. The organic extract is washed with water, brine, dried over Na_2SO_4 , filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (from 100% hexanes to 20% ethyl acetate in hexanes) eluting the title compound (45.8 mg, 75% yield) as an oil. ES-MS (m/z): calcd $[\text{M} + \text{H}]^+$: 380.17; analysis 381.1 ($\text{M} + \text{H})^+$. ^1H NMR (400 MHz, CDCl_3): δ 7.83 (d, $J = 3.5$ Hz, 1H), 7.29 (d, $J = 3.1$ Hz, 1H), 7.20 (s, 1H), 6.68 (br s, 1H), 3.35 (br s, 1H), 2.53 (s, 3H), 2.49 (s, 3H), 2.40 (s, 3H), 1.90-1.76 (m, 4H), 0.86 (t, $J = 7.5$ Hz, 6H).

Example 229

8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl)-imidazo [1,2-*b*] Preparation of compounds having pyridazine and methanesulfonic acid

8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo [1,2-*b*] pyridazine (0. To a solution of 55 g, 1.36 mmol) and MeOH (6 mL) is added methanesulfonic acid (0.088 mL, 1.36 mmol). After 1 hour, the solution is concentrated and the solution is treated with Darco-60 for 1 hour, filtered and concentrated to yield the title compound (0.68 g, 1.36 mmol, > 99%). ^1H NMR (CDCl_3): δ 0.85 (t, $J = 7.4$ Hz, 6H), 1.67-1.91 (m, 4H), 1.96 (s, 3H), 1.97 (s, 3H), 2.20 (s, 3H), 2.61 (s, 3H), 2.99 (s, 3H), 3.17-3.29 (m, 1H), 7.33 (s, 1H), 7.64 (d, $J = 7.4$ Hz, 1H), 7.89 (d, $J = 7.9$ Hz, 1H), 8.18 (s, 1H), 8.34 (t, $J = 7.9$ Hz, 1H), 9.95 (bs, 1H). LC / MS (m/z): calcd $[\text{M} + \text{H}]^+$: 405.6; ANALYSIS: 405.6.

Example 230

Of 3-(8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-*b*] pyridazin-3-yl)-4-methyl-thiophen-3-yl)-dimethyl-amine Preparation

To a -78°C solution of dimethyl-(4-methyl-thiophen-3-yl)-amine (0.43 g, 3.06 mmol) and THF (5 mL) was added 1.6M n-BuLi (1.91 mL, 3.06 mmol). The solution is stirred for 1 hour, then 0.5M ZnCl_2 (6.1 mL, 3.06 mmol) is added and the solution is heated to room temperature. After 30 minutes, 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo [1,2-*b*] pyridazine (0.70 g, 2.04 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.075 g, 0.10 mmol) is added and the solution is heated at 65°C overnight. The solution is diluted with EtOAc (35 mL), washed with saturated NH_4Cl (30 mL), dried over MgSO_4 , filtered and concentrated. The residue is purified by ISCO flash chromatography (15% to 30% EtOAc gradient) to yield the title compound (0.13 g, 0.36 mmol, 18%). ^1H NMR (CDCl_3): δ 0.86 (t, $J = 7.5$ Hz, 6H), 1.72-1.90 (m, 4H), 2.03 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 2.77 (s, 6H), 3.28-3.37 (m, 1H), 6.63 (s, 1H), 6.65 (s, 1H). LC / MS (m/z): calcd $[\text{M} + \text{H}]^+$: 357.2; ANALYSIS: 357.2.

Example 231

3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-8-(1-Ethyl-propyl)-imidazo [1,2-*b*] pyridazine Preparation of propyl-butyl-imidazo [1,2-*b*] pyridazine

2,5-Dimethyl-8-(1-propyl-butyl)-imidazo [1,2-b] pyridazine (below) (0.30 g, 1.22 mmol), 5-(5-bromo-4-chloro-thiophene)-2-yl-1-methyl-[1,2,4] triazole (below) (0.41 g, 1.47 mmol), KOAc (0.60 g, 6.11 mmol), TBAH (0.39 g, 1.22 mmol) and a slurry of NMP (3 mL) are degassed with N₂ for 30 min. Pd(OAc)₂ (0.014 g, 0.061 mmol) and TDBPP (0.040 g, 0.061 mmol) are added and the solution is heated at 125 °C. for 2.5 hours. The solution is diluted with EtOAc (50 mL), washed with water (3 × 50 mL), brine (50 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%–40% EtOAc gradient) to yield the title compound (0.30 g, 0.68 mmol, 56%). ¹H NMR (CDCl₃) δ 0.89 (t, J = 7.4 Hz, 6H), 1.14–1.39 (m, 4H), 1.76 (q, J = 16.3, 7.7 Hz, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.41–3.50 (m, 1H), 4.15 (s, 3H), 6.73 (s, 1H), 7.46 (s, 1H), 7.90 (s, 1H). LC / MS (m/z): calcd [M + H]⁺: 443.2; ANALYSIS: 443.3.

Example 232

(2-(4-Chloro-5-(5-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazin-3-yl)-thiophen-2-yl)-pyro [Ru-1-yl]-dimethyl-amine) preparation
Using a procedure similar to Example 27, 1-(dimethylamino)-pyrrole (0.20 mL, 1.65 mmol), THF (4 mL), 1.5 M n-BuLi (1.10 mL, 1.73 mmol), a 5M ZnCl₂ (3.46 mL, 1.73 mmol), 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl From the imidazo [1,2-b] pyridazine (0.34 g, 0.82 mmol) and PdCl₂(dppf) (0.030 g, 0.041 mmol), the title compound (0.17 g, 0.38 mmol, 46%) is generated. ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74–1.92 (m, 4H), 2.52 (s, 6H), 2.84 (s, 6H), 3.28–3.39 (m, 1H), 6.21 (dd, J = 4.1, 5.2 Hz, 1H), 6.38 (dd, J = 4.1) 1.8 Hz, 1H), 6.68 (s, 1H), 7.02 (dd, J = 3.2, 1.8 Hz, 1H), 7.29 (s, 1H). LC / MS (m/z): calcd [M + H]⁺: 442.2; ANALYSIS: 442.3.

Example 233

3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-8-iodo-2,6-dimethyl-Preparation of imidazo [1,2-b] pyridazine
A. The reaction flask of 4-chloro-thiophene-2-carbonitrile 22L is equipped with a cooling bath, an air stirrer, a gas addition tube, and a thermometer probe. Remove nitrogen from the flask and fill with AlCl₃ (1025 g, 7.69 moles) and CHCl₃ (6.6 L, 16.5 vol). After the mixture has been cooled to 0–5 °C, the temperature is maintained below -10 °C and 2-thiophenecarbonitrile (400 g, 3.66 moles) is added dropwise via a dropping funnel for 10–15 minutes. The mixture is filled with Cl₂ gas (300 g, 4.23 moles, 1.16 EQ) for less than -10 °C, under water for 1.25 hours. The course of the reaction is monitored by GC (GC sampling is by quenching an aliquot of the reaction mixture with 6N HCl, extracted with EtOAc, dried over Na₂SO₄, filtered and the filtrate is filtered, inject. When the reaction is considered to be completed by GC analysis [when the ratio of (sm: prod: dichloro) in area% GC is approximately (1: 5.8: 1), the reaction is considered completed.], 6N HCl (8.0 L) is added dropwise via the addition funnel for 1.5 hours, while maintaining the temperature below -20 °C [HCl addition is very exothermic and outgassing]. Transfer the reaction to a separatory funnel and separate the layers. After extracting the aqueous layer with CHCl₃ (4.0 L), the chloroform layer is mixed and washed with deionized H₂O (6.0 L). The organic layer is dried over Na₂SO₄, filtered and concentrated in vacuo to produce 575 g, 109.3% pale yellow semi-solid. According to GC (temperature gradient 60 °C to 280 °C) area% analysis, 76% product with numerous impurities (ret = 6.5 min) is unreacted starting material (ret = 5.1 min) and The dichloride product (ret = 7.4 min). GC Method: Column: DB1; Injector = 300 °C; T_{initial} = 60 °C; t = 2.0 min; T_{final} = 280 °C; rate = 18 °C/min 4-Chloro-2-thiophenecarboxamide. A 12 L reactor flask equipped with a cooling bath, air stirrer and thermometer probe was filled with KOH (288.6 g, 5.143 moles) and deionized H₂O (5.04 L) to 73 °C. An exothermic solution is formed. After cooling the solution to 28.0 °C, the mixture was filled with 4-chloro-2-thiophenecarbonitrile (671.3 g, 4.675 moles) [a small amount of solid is undissolved at this point] And then filled with EtOH (675 mL). A gentle gradient exotherm occurs with the addition of EtOH and lasts for more than 1 to 1.5 hours until 38 °C is reached. The reaction is stirred overnight at room temperature. The reaction mixture is filtered under vacuum, washed with deionized H₂O and dried to produce the crude product. The solid is dissolved in EtOAc and treated with Na₂SO₄ and Darco for 1–2 hours, then filtered and washed with EtOAc (10.0 L). Concentrate the filtrate on Buchi at 45 °C until the solid begins to precipitate out of vacuum and re-melt the solid by raising the temperature to 60–65 °C. While stirring at 60 °C, heptane (3.5 L) is slowly added to precipitate the solid. After stirring at 60 °C for 15–20 minutes, the mixture is cooled to 30–40 °C and filtered. The solid was washed with heptane (2 × 0.75 L) and dried to give the title compound (ret = 9.9) as a white solid (235.4 g, 31.2%, 96.4 area% according to GC analysis). Min). A second crop is obtained from the filtrate to yield 67.8 g, 9.0%, 94.5% area% according to GC analysis. The overall yield is 303.2 g (40.1%).
C. 4-Chloro-N-dimethylaminomethylene-2-thiophenecarboxamide A 5-L reaction flask equipped with a heating mantle, an air stirrer, a Dean-stark device and a thermometer probe was added to 4-chloro-2-thiophene. Fill with carboxamide (360 g, 1.856 moles) and dimethylformamide dimethylacetate (872 mL) and form a slurry from its endothermic 1–2 °C to 22–26 °C. Collect the distillate (mostly MeOH) and gradually heat the mixture to 96 °C. Remove the heating mantle and cool the mixture to below -25 °C. Deionized H₂O (3.0 L) is added via a dropping funnel to maintain the temperature below -35 °C. The reaction mixture is extracted with EtOAc (1 × 3.0 L, 1 × 1.5 L), then mixed and the organic fertilizer is washed with deionized H₂O (1.5 L). The organic phase is dried over Na₂SO₄, filtered and concentrated in vacuo to produce the crude product (400 g). The crude product is dissolved in EtOAc (320 mL, 0.8 Vol) at 50–60 °C, then the temperature is gradually raised to 70 °C and heptane (1700 mL, 4.25 Vol) is added slowly. Add seed crystals (Lot: PP6-H00085-075-1) to the cloudy solution and begin precipitation. The resulting mixture is stirred overnight at room temperature, then filtered and washed with heptane. The solid is dried to yield the title compound (ret = 13.0 min) as a white solid (329.8 g, 82%, 98.2% area% according to GC analysis).
D. 5-(4-Chloro-thiophen-2-yl)-1-methyl-1H-[1,2,4] triazole A 3 L reaction flask equipped with a cooling bath, an air stirrer and a thermometer probe. Fill with 4-chloro-N-dimethylaminomethylene-2-thiophenecarboxamide (155 g, 0.715 moles) and HOAc (1500 mL) to form a solution. Methylhydrazine (33.2 g, 0.721 moles) is added dropwise via a dropping funnel for 15–20 minutes using an ice water cooling bath to maintain the temperature below -30 °C to form a pale yellow slurry. Gradually heat the reaction to 90 °C and hold at 90 °C for 30 minutes. After analysis of the mixture by GC, the reaction is cooled to 70 °C and then concentrated to a thick oil / slurry. Slowly add deionized H₂O (1.67 L) to precipitate the solid, then cool the mixture to <30 °C, filter and wash with deionized H₂O (1.67 L). The wet solid (125.8 g) is redissolved in warm MTBE (1.64 L), dried over Na₂SO₄, filtered and concentrated to dryness to give a pale yellow solid (85.8 g, 69.1%, 91.9% area% according to GC) to yield the title compound.

E. 3 L with 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-1H-[1,2,4] triazole cooling bath, air stirrer and thermometer probe The reaction flask was charged with 5-(4-chloro-thiophen-2-yl)-1-methyl-1H-[1,2,4] triazole (105.3 g, 0.527 moles), ACN (1053 mL). And fill with HOAc (105 mL) to form a solution. NBS (103.2 g, 0.569 moles) is partially added over 30–60 minutes while maintaining the temperature below -31 °C. After stirring for 1 hour [reaction temperature dropped to 26.7 °C after 1 hour] GC analysis indicated the reaction was complete. The reaction mixture is poured into deionized H₂O (2.1 L, 20 vol), stirred for 30 minutes, filtered and washed with deionized H₂O (2 × 1 L). The product is dried overnight at 45 °C in a vacuum oven to yield the title compound as a pale yellow solid (123.0 g, 83.8%, 96.6% area% according to GC).

F. 2,6-Dimethyl-imidazo [1,2-b] pyridazine 3-neck 1 L round bottom flask was prepared with 5-methyl-pyridazin-3-ylamine (20 g, 0.18 moles) ethanol 2B (200 mL) and chloroacetone. (23.7 g, 0.204 mL, 0.256 moles, 1.4 eq). The reaction mixture is heated at 70 °C overnight. NaHCO₃ (23.2 g, 0.276 moles, 1.5 eq) is added in portions. After most of the boiling phenomenon has subsided, the reaction is heated at 100 °C overnight. The solvent is removed in vacuo and the residue is dissolved in dichloromethane and filtered through filter paper. The solvent is removed again in vacuo. The residue is purified using silica gel chromatography with a hexane: ethyl acetate gradient to yield the title compound (15.5 g, 57%). ¹H-NMR (DMSO-d₆) δ 2.34 (s, 3H), 2.47 (s, 3H), 7.03, (d, J = 10 Hz, 1H), 7.85 (d, J = 10 Hz, 1H), 7.91 (s, 1H) ppm. MS (APCI): 148 (M + 1).

G. 3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo [1,2-B] pyridazine 2,6-dimethyl-imidazo [1,2-b] pyridazine (0.32 g, 2.17 mmol), 5-(5-

bromo-4-chloro-thiophen-2-yl)-1-methyl A solution of 1-H-[1,2,4] triazole (0.72 g, 2.61 mmol), Cs₂CO₃ (1.49 g, 4.57 mmol) and DMF (6 mL) was added with N₂ to 15 Degas. Pd(OAc)₂ (0.024 g, 0.11 mmol) and PPh₃ (0.057 g, 0.22 mmol) are added and the solution is heated at 135 °C. for 4 hours. The solution is diluted with CH₂Cl₂ (50 mL), washed with saturated NH₄Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30% to 100% EtOAc gradient) to yield the title compound (0.29 g, 0.84 mmol, 39%). ¹H NMR (CDCl₃) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). LC / MS (m/z): calcd C₁₅H₁₃N₃OS (M + H)⁺: 345.1; ANALYSIS: 345.2.

H-3-(3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl)-8-iodo-2,6-dimethyl-imidazo [1,2-b] pyridazine. 3-(3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl)-2,6-dimethyl-imidazo [1,2-b] To a -78 [deg.] C solution of pyridazine (1.50 g, 4.35 mmol) and THF (50 mL) is added I₂ (1.21 g, 4.78 mmol). After 10 minutes, 2M LDA (5.44 mL, 10.87 mmol) is added. The solution was stirred for 30 min, quenched with water, diluted with EtOAc (100 mL), washed with water (100 mL), saturated Na₂S₂O₃ (100 mL), brine (100 mL), dried over MgSO₄, Filter and concentrate. The residue is purified by ISCO flash chromatography (100% EtOAc) to yield the title compound (0.61 g, 1.39 mmol, 35%). ¹H NMR (CDCl₃) δ 2.50 (s, 3H), 2.55 (s, 3H), 4.14 (s, 3H), 7.47 (s, 1H), 7.51 (s, 1H), 7.89 (s, 1H). LC / MS (m/z): calcd C₁₅H₁₂ClN₄OS (M + H)⁺: 471.0; ANALYSIS: 471.0.

Example 234

3-(3-Chloro-5-(2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

A. 5-(4-Chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-1H-[1,2,4] triazole 4-chloro-N-dimethyl A solution of aminomethylene-2-thiophenecarboxamide (1.00 g, 4.62 mmol) and AcOH (1 mL) in 75% water-soluble 2,2,2-trifluoroethyl-hydrazine (0.79 mL, 4.65 mmol) is added. The solution is heated at 90 °C. for 40 min, concentrated, dissolved in Et₂O (40 mL), washed with water (30 mL), saturated NaHCO₃ (30 mL), dried over MgSO₄, filtered and concentrated. To yield the title compound (1.24 g, 4.62 mmol > 99%). ¹H NMR (CDCl₃) δ 4.88 (q, J = 16.6, 7.6 Hz, 2H), 7.26 (d, J = 0.9 Hz, 1H), 7.31-7.33 (m, 1H), 7.94 (s, 1H). LC / MS (m/z): Calculated C₁₅H₁₄BrClF₃N₃S (M + H)⁺: 268.0; ANALYSIS: 268.0.

B. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-1H-[1,2,4] triazole 5-(4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-1H-[1,2,4] triazole (1.13 g, 4.22 mmol) Br₂ (0.23 mL, 4.43 mmol) is added to the solution and AcOH (10 mL) in a shield tube. The solution is heated at 120 °C. for 2 hours and 140 °C. for 5 hours. The solution was concentrated, diluted with Et₂O (150 mL), washed with saturated NaHCO₃ (75 mL), saturated Na₂S₂O₃ (75 mL), brine (75 mL), dried over MgSO₄, filtered. Concentrate. The residue is purified by ISCO flash chromatography (5%-15% EtOAc gradient) to yield the title compound (1.04 g, 3.09 mmol, 71%). ¹H NMR (CDCl₃) δ 4.88 (q, J = 16.0, 7.9 Hz, 2H), 7.22 (s, 1H), 7.9 (s, 1H). LC / MS (m/z): Calculated C₁₅H₁₄BrClF₃N₃S (M + H)⁺: 345.9; Analytical value: 346.0.

C. 3-(3-Chloro-5-(2-(2,2,2-trifluoro-ethyl)-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine Using a procedure analogous to Example 231, 8-(1-ethyl-propyl)-2,6-Dimethyl-imidazo [1,2-b] pyridazine (0.25 g, 1.14 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-1H-[1,2,4] triazole (0.47 g, 1.37 mmol), KOAc (0.56 g, 5.60 mmol), TBAH (0.37 g, 1.14 mmol) and NMP (3 mL), Pd(OAc)₂ (0.01 g, 0.057 mmol) and TDBPP (0.037 g, 0.057 mmol) produce the title compound (0.43 g, 0.89 mmol, 78%). ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 4.98 (q, J = 15.7, 7.9 Hz, 2H), 6.74 (s, 1H), 7.45 (s, 1H), 8.03 (s, 1H). LC / MS (m/z): calcd C₂₁H₂₂ClF₃N₄S (M + H)⁺: 483.1; ANALYSIS: 483.2.

Example 235

3-(5-(2-tert-Butyl-2H-[1,2,4] triazol-3-yl)-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

A. 1-tert-Butyl-5-(4-chloro-thiophen-2-yl)-1H-[1,2,4] using a procedure analogous to triazole Example 234A, using 4-chloro-N- From dimethylaminomethylene-2-thiophenecarboxamide (5.00 g, 23.07 mmol) and AcOH (50 mL), tert-butylhydrazine hydrochloride (3.16 g, 25.38 mmol), the title compound (0.20 g, 0.83 mmol, 3.6%). ¹H NMR (CDCl₃) δ 1.63 (s, 9H), 7.07 (d, J = 1.3 Hz, 1H), 7.51 (d, J = 1.3 Hz, 1H), 8.08 (s, 1H).

B. Triazole Example 249B of 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-1H-[1,2,4] 1-tert-butyl-5-(4-chloro-thiophen-2-yl)-1H-[1,2,4] triazole (0.20 g, 0.83 mmol) using a procedure similar to), AcOH (3 mL) and Br₂ (0.051 mL, 0.99 mmol) to yield the title compound (0.27 g, 0.83 mmol > 99%). ¹H NMR (CDCl₃) δ 1.62 (s, 9H), 7.42 (s, 1H), 8.08 (s, 1H). LC / MS (m/z): calcd C₁₅H₁₄BrClF₃N₃S (M + H)⁺: 320.0; ANALYSIS: 320.0.

C. 3-(5-(2-tert-Butyl-2H-[1,2,4] triazol-3-yl)-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-Dimethyl-imidazo [1,2-b] pyridazine Using a procedure analogous to Example 231, using 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] Pyridazine (0.15 g, 0.68 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-1H-[1,2,4] triazole (0.20 g, 0.82 mmol), KOAc (0.34 g, 3.42 mmol), TBAH (0.22 g, 0.68 mmol) and NMP (3 mL), Pd(OAc)₂ (0.0677 g, 0.034 mmol) and TDBPP (0.022 g, 0.034 mmol) yield the title compound (0.039 g, 0.085 mmol, 13%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.65 (s, 9H), 1.73-1.91 (m, 4H), 2.51 (s, 6H), 3.26-3.37 (m, 1H), 6.69 (s, 1H), 7.65 (s, 1H), 8.11 (s, 1H). LC / MS (m/z): calcd C₂₃H₂₇ClN₄OS (M + H)⁺: 457.2; ANALYSIS: 457.3.

Example 236

3-(3-Chloro-5-[1,2,4] triazol-1-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] Preparation of pyridazine

A. 3-(3-Chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine under nitrogen 10 mL anhydrous of CH₃CN 3-(3-chloro -thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl -imidazo [1,2-b] pyridazine (2 g, 6 mmol) To this solution is partially added NIS (1.6 g, 7.2 mmol). The reaction mixture is stirred at reflux for 14 hours. After cooling, the solvent is concentrated in vacuo and the residue is dissolved in EtOAc and washed with H₂O, a 5% solution of sodium bisulfite, H₂O and brine. The organic layer is dried over magnesium sulfate, filtered and concentrated in vacuo. The crude residue is purified by silica gel chromatography using 8:2 hex / EtOAc as eluent mixture to yield 2.4 g of the title compound. Mass spectrum 460 (M + 1). ¹H-NMR (CDCl₃, 300 MHz) δ 7.24 (s, 1H), 6.71 (s, 1H), 3.32 (q, 1H, J = 7.2) Hz), 2.52 (s, 3H), 2.49 (s, 3H), 1.84 (q, 4H, J = 7.2 Hz), 0.88 (t, 6H, J = 7.2) Hz) ppm.

B. 3-(3-Chloro-5-[1,2,4] triazol-1-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine 3-(3-chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] Pyridazine (0.50 g, 0.65 mmol), 1H-triazole (0.047 g, 0.69 mmol), CuI (0.0062, 0.033 mmol), Cs₂CO₃ (0.45 g, 1.37 mmol) And (1S, 2S)-(+)-N, N-dimethylcyclohexane-1,2-diamine (0.014 mL, 0.098 mmol) is added to a solution of DMF (3 mL). The solution is heated at 112 °C. overnight, diluted with CH₂Cl₂ (10 mL), filtered through Celite® and concentrated. The residue is purified by ISCO flash chromatography (30% to 40% EtOAc gradient) to yield the title compound (0.028 g, 0.070 mmol, 11%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.35 (m, 1H), 6.72 (s, 1H), 7.22 (s, 1H), 8.10 (s, 1H), 8.50 (s, 1H). LC / MS (m/z): calcd C₁₉H₂₁ClN₄S (M + H)⁺: 401.1; ANALYSIS: 401.2.

Example 237

3-(3-Chloro-5-(2,5-dimethyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine

3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.30 g, 0.72 mmol) and THF (5 mL) in a -78 ° C. solution to 1.7 M tert-BuLi (0.47 mL, 0.80 mmol) Add. After 15 minutes, MeI (0.052 mL, 0.83 mmol) is added and the solution is heated to room temperature. The solution is diluted with EtOAc (40 mL), washed with brine (40 mL), dried over MgSO₄, filtered and concentrated. The solution is recrystallized from acetone: hexane to produce the title compound (0.13 g, 0.30 mmol, 42%). ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.36 (s, 3H), 2.51 (s, 6H), 3.27-3.39 (m, 1H), 3.40 (s, 3H), 6.72 (s, 1H), 8.02 (s, 1H). LC / MS (m / z): calcd (C₂₁H₂₂N₄OS) (M + H)⁺: 429.2; ANALYSIS: 429.2.

Example 238

3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
A. N-(6-methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide 3-chloro-6-methoxy-pyridazine (10.0 g (59.18 mmol) was added to 2,2-dimethyl-propion. Mix with Cs₂CO₃ (33.8 g, 103.77 mmol) in amide (8.40 g, 83.01 mmol), BINAP (2.15 g, 3.46 mmol), 1,4-dioxane (150 mL). Degas with N₂ for 10 minutes at room temperature. Pd₂(dba)₃ (3.16 g, 3.46 mmol) is added and the resulting mixture is refluxed overnight. The mixture is cooled to room temperature, diluted with EtOAc (150 mL), filtered through silica gel and washed with EtOAc (2 × 150 mL). The filtrate is washed with H₂O (2 × 300 mL), dried over MgSO₄, filtered and concentrated. Purification of the crude material by silica gel chromatography yields the title compound (6.59 g, 31.53 mmol, 45%). ¹H NMR (CDCl₃) δ: 1.35 (s, 9H), 4.03 (s, 3H), 7.01 (d, J = 9.7 Hz, 1H), 8.41 (d, J = 9.7 Hz, 1H), 8.44 (s, 1H). ES-MS (m / z): calcd (C₂₄H₂₆N₄O₂) (M + H)⁺: 210.3; ANALYSIS: 210.1.

8-N-[4-(1-Ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide Using a procedure analogous to Example 6a, 3-pentyl bromide (16.4N-(6-methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide (6.09 g, 29.9 mmol) prepared from 1 mL, 160.3 mmol) and magnesium (3.84 g, 160.26 mmol), 14 mmol) and the Grignard reagent yield the title compound (5.32 g, 19.08 mmol, 65%). ¹H NMR (CDCl₃) δ: 0.84 (t, J = 7.5 Hz, 6H), 1.36 (s, 9H), 1.50-1.72 (m, 4H), 3.50-3.70 (m, 1H), 4.07 (s, 3H), 6.96 (s, 1H). ES-MS (m / z): calcd (C₂₈H₃₂N₄O₂) (M + H)⁺: 280.4; ANALYSIS: 280.2.

C. N-[4-(1-Ethyl-propyl)-6-methoxy- in 4-(1-ethyl-propyl)-2-methoxy-6-methyl-pyrrolo [1,2-b] pyridazine EtOH (250 mL). A solution of pyridazin-3-yl)-2,2-dimethyl-propionamide (5.32 g, 19.08 mmol) is treated with ZnCl₂ (26.0 g, 190.8 mmol) and refluxed for 48 hours. The reaction is cooled to room temperature and concentrated. The residue is occupied with EtOAc (250 mL) and H₂O (100 mL). The residue is washed with H₂O (2 × 100 mL), dried over Na₂SO₄, filtered and concentrated. The residue is then dissolved in EtOAc (80 mL), refluxed overnight and reacted with chloroacetone (1.6 mL, 20.03 mmol). NaHCO₃ (8.10 g) is added while hot and the reaction is refluxed for 1 hour. Cool to room temperature, filter through silica gel washed with EtOAc and concentrate. Purification of the crude material by chromatography produces the title compound (0.48 g, 2.97 mmol, 11%). ¹H NMR (CDCl₃) δ: 0.84 (t, J = 7.5 Hz, 6H), 1.69-1.869 (m, 4H), 2.45 (s, 3H), 3.19-3.30 (m, 1H), 3.94 (s, 3H), 6.39 (s, 1H), 7.49 (s, 1H). ES-MS (m / z): calcd (C₁₈H₂₀N₄O₂) (M + H)⁺: 233.3; ANALYSIS: 234.1.

D. 3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine. 4-(1-ethyl-propyl)-2-methoxy-6-methyl-pyrrolo [1,2-b] pyridazine (74.8 mg, 0.32 mmol), 5-(5-bromo-4-chloro-thiophene-2-yl)-1-methyl-1H-[1,2,4] triazole (107.5 mg, 0.33 mmol), TD8PP (10.4 mg, 0.016 mmol), tetrabutylammonium bromide (103.0 mg, 0.32 mmol), KOAc (158 mg, 1.61 mmol) in NMP (15 mL) is removed with N₂ for 5 min. Pd(OAc)₂ (3.6 mg, 0.016 mmol) is added and the resulting mixture is stirred at 125 ° C. for 6 hours. The reaction is cooled to room temperature, diluted with EtOAc (10 mL), filtered through silica gel and washed with EtOAc (3 × 30 mL). The filtrate is washed with H₂O (3 × 30 mL), dried over Na₂SO₄, filtered and concentrated. Purification of the crude material by silica gel chromatography yields the title compound (0.1006 g, 0.2469 mmol, 77%). ¹H NMR (CDCl₃) δ: 0.89 (t, J = 7.6 Hz, 6H), 1.75-1.90 (m, 4H), 2.52 (s, 3H), 3.22-3.38 (m, 1H), 3.93 (s, 3H), 4.15 (s, 3H), 6.52 (s, 1H), 7.48 (s, 1H), 7.91 (s, 1H). ES-MS (m / z): calcd (C₂₀H₂₂N₄OS) (M + H)⁺: 431.9; ANALYSIS: 431.9.

Example 239

3-[3-Chloro-5-(5-fluoro-2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
Preparation of propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
3-[3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (0.40 g, 0.72 mmol) and THF (8 mL) in a -78 ° C. solution to 1.7 M tert-BuLi (0.47 mL, 0.80 mmol) is added. After 30 minutes, the solution is transferred via cannula to a solution of N-fluorobenzenesulfonamide (0.40 g, 1.25 mmol) and THF. After 30 minutes, the solution is heated to room temperature. The solution is diluted with EtOAc (40 mL), washed with water (30 mL), brine (30 mL), dried over MgSO₄, filtered and concentrated. The solution is purified by ISCO (20% -30% EtOAc gradient) to yield the title compound (0.068 g, 0.16 mmol, 16%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.71-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.26-3.36 (m, 1H), 4.08 (d, J = 2.7 Hz, 3H), 6.75 (s, 1H), 7.97 (s, 1H). LC / MS (m / z): calcd (C₂₂H₂₂N₄OS) (M + H)⁺: 433.2; ANALYSIS: 433.2.

Example 240

Preparation of the preparation of 3-(4,5-dibromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
3-(5-Bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (5.92 g, 14.1 mmol) is added to a solution of 34 mmol) and trifluoroacetic acid (40 mL) and 98% H₂SO₄ (10 mL). After 10 minutes, the solution is poured onto ice and becomes basic with 5M NaOH. The slurry is extracted with EtOAc (3 × 100 mL) and the combined organic layers are washed with water (2 × 400 mL), brine (400 mL), dried over MgSO₄, filtered and concentrated to give the title compound (6.61 g, 13.44 mmol, 94%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.47 (s, 3H), 2.52 (s, 3H), 3.25-3.34 (m, 1H), 5.72 (s, 1H). LC / MS (m / z): calcd (C₁₇H₁₆Br₂OS) (M + H)⁺: 489.9; ANALYSIS: 490.0.

Example 241

Preparation of 3-(4-Bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
Using a procedure similar to that in Example 76, 3-(4,5-dibromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine (1.83 g, 3.72 mmol), 1.6M n-BuLi (2.56 mL, 4.09 mmol) and THF (30 mL) from the title compound (1.05 g, 2.54 mmol, 68%). ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.48 (s, 3H), 2.51 (s, 3H), 3.27-3.36 (m, 1H), 6.71 (s, 1H), 7.55 (s, 1H). LC / MS (m / z): calcd (C₁₇H₁₆BrOS) (M + H)⁺: 412.0; ANALYSIS: 412.1.

Example 242

Preparation of 3-(1-methyl-3-phenyl-1H-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo [1,2-b] pyridazine
A. 1-methyl-3-phenyl-1H-pyrazole - le and 1-methyl-5-phenyl-1H-pyrazole - Sodium le hydride (mineral oil, 0.93 g, 60% of the variance of 20.8 mmol), Suspend in THF (45 mL) and stir under nitrogen atmosphere. 3-Phenylpyrazole (2.5 g, 17.3 mmol dissolved in THF, 15 mL) is added slowly and stirred for 30 minutes, then iodomethane (1.3 mL, 20.8 mmol) is added. Stir for 3 hours. The reaction is added to water and extracted twice with ethyl acetate. The combined organic extract is washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (40% ethyl acetate to 100% hexane in hexane) to elute the title compound. 1-methyl-3-phenyl-1H-pyrazole - le and 1-methyl-5-phenyl-1H-pyrazole - obtaining a mixture of le (2.6 g, 95% yield).

B. 4-bromo-1-methyl-3-phenyl-1H-pyrazole-1-ol and 4-bromo-1-methyl-5-phenyl-1H-pyrazole-1-ol isomers, 1-methyl-3-phenyl-1H-pyrazole-1-ol and 1-methyl-5-phenyl-1H-pyrazole-1-ol (1.0g, 6.3mmol) NBS (1.1g, 6.3mmol) the mixture was mixed in acetonitrile (25 ml), stirred then, heat at 70 ° C. for 1 hour. The solution is concentrated and the crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 25% ethyl acetate in hexane), respectively, to give 4-bromo-1-methyl-3-phenyl-1H-pyrazole (304 mg, 34% yield) and 4-bromo-1-methyl-5-phenyl-1H-pyrazole (295 mg, 20% yield) are eluted. ¹H NMR: (400 MHz, DMSO): (trademark) 8.01 (s, 1H), 7.95 (d, 2H), 7.41 (t, 2H), 7.38 (d, 1H), 3.85 (s, 3H). ¹H NMR: (400 MHz, DMSO): (trademark) 7.63 (s, 1H), 7.50 (m, 5H) 3.77 (s, 3H). C. 3-(1-Methyl-3-phenyl-1H-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine 8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-3-phenyl-1H-pyrazole (250 mg, 1.1 mmol) and cesium carboxylate (490 mg, 1.50 mmol) are stirred with DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. PdCl₂(PPh₃)₂ (15 mg) is added and the mixture is heated at 130 ° C. overnight. The mixture is added to water and extracted twice with ethyl acetate. The combined organic extract is dried over Na₂SO₄, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (from 100% hexane to 50% ethyl acetate in hexane) to elute the title compound (17.5 mg, 4% yield). ES-MS (m/z): calcd 374.5; analysis 374.2 (M + H)⁺. ¹H NMR (400 MHz, CDCl₃): (trademark) 7.68 (s, 1H), 7.37 (m, 2H), 7.20 (m, 3H), 6.59 (s, 1H), 4.94 (s, 3H), 3.36 (m, 1H), 2.38 (s, 3H), 2.15 (s, 3H), 1.82 (m, 4H), 0.86 (t, 6H).

Example 243

Preparation of 3-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine

Using a procedure analogous to Example 242, 8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-5-phenyl-1H-pyrazole-1-ol (250mg, 1.1mmol), carboxylic acid cesium (490 mg, 1.50 mmol) and from DMF (5 ml) medium PdCl₂(PPh₃)₂ (15mg), the title compound (18 mg, 4% yield). ES-MS (m/z): calcd 374.5; analysis 374.2 (M + H)⁺. ¹H NMR (400 MHz, CDCl₃): (trademark) 7.65 (s, 1H), 7.32 (m, 3H), 7.23 (m, 2H), 6.55 (s, 1H), 3.94 (s, 3H), 3.27 (m, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.76 (m, 4H), 0.83 (t, 6H).

Example 244

Preparation of 3-(3,5-dimethylisoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine

Using a procedure similar to Example 242, 8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine (200 mg, 0.90 mmol), 4-bromo-3, PdCl₂(PPh₃)₂ (25 mg) in 5-dimethylisoxazole (Alfa, 320 mg, 1.8 mmol), cesium carboxylate (880 mg, 2.70 mmol) and DMF (5 ml) at 130 ° C. Heat for 4 hours, then produce the title compound (65 mg, 23% yield) at room temperature overnight. ES-MS (m/z): calcd 312.4; analysis 313.2 (M + H)⁺. ¹H NMR (400 MHz, CDCl₃): (trademark) 6.68 (s, 1H), 3.32 (m, 1H), 2.50 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H), 1.82 (m, 4H), 0.87 (m, 6H).

Example 245

Preparation of 3-(3-methyl-5-phenyl-isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine

A. 4-Bromo-3-methyl-5-phenylisoxazole 3-methyl-5-phenylisoxazole (Synthesis, 1997, 439-442) (1.0 g, 6.3 mmol) and N-bromo Succinimide (1.2 g, 6.9 mmol) is mixed with acetic acid (30 ml) together and heated at reflux for 2 hours. The solution is added to water and extracted twice with ethyl acetate. The combined organic extracts are washed with sodium bicarbonate (saturated) and saturated NaCl, then dried over Na₂SO₄, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (10% ethyl acetate to 100% hexane in hexane) to elute the title compound (1.5 g, 100% yield). ¹H NMR (400 MHz, CDCl₃): (trademark) 8.02 (m, 2H), 7.49 (m, 3H), 6.34, 2.35 (s, 3H). B. 3-(3-Methyl-5-phenyl-isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine Similar to Example 257 8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine (200 mg, 0.90 mmol), 4-bromo-3-methyl-5-phenyl Mix isoxazole (430 mg, 1.8 mmol), cesium carboxylate (880 mg, 2.70 mmol) and PdCl₂(PPh₃)₂ (25 mg) in DMF (5 ml) and heat at 130 ° C. for 5 hours. To yield the title compound (65 mg, 23% yield). ES-MS (m/z): calcd 374.5; analysis 375.1 (M + H)⁺. ¹H NMR (400 MHz, CDCl₃): (trademark) 7.50 (d, 2H), 7.31 (m, 3H), 6.69 (s, 1H), 3.39 (m, 1H), 2.48 (s, 3H), 2.20 (s, 6H), 2.33 (s, 3H), 1.84 (m, 4H), 0.88 (m, 6H).

Example 246

{5-[8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dipropyl-amine

35 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine (0.09 mmol) and 45 mg di-n-propylamine (0.44 mmol) and 57 mg cesium carboxylate (0.18 mmol) are placed in a 4 ml reaction vial with 3 ml dry THF and the vial is covered with a Teflon cap. The reaction vial is heated at 100 ° C. for 4 hours. Transfer the reaction mixture to a microwave reactor and seal. The reaction mixture is heated in the microwave at 160 ° C. for 30 minutes. The mixture is concentrated and applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1) to produce the title compound. 5.3 mg (14%); mass spectrum (m/e): 414; ¹H-NMR (CDCl₃): 5.59 (s, 1H), 3.45 (m, 4H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 1.80 (m, 8H), 0.99 (t, 6H, J = 7.5 Hz), 0.89 (t, 6H, J = 9.4 Hz).

Example 247

N-{5-[8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazin-3-yl]-4-chloro-thiazol-2-yl}-Dimethylamine, mesylate

89 mg N-{5-[8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazin-3-yl]-4-chloro-thiazol-2-yl}-Dimethylamine (0.236 mmol) is dissolved in 2.0 ml of ethyl acetate and 0.236 ml of 1M methanesulfonic acid in ethyl acetate (0.236 mmol) is added. The solvent is removed under N₂ gas and the precipitated crystals are collected, washed with Et₂O and dried. 92 mg (83%); mass spectrum (m/e): 378 (M + 1); ¹H-NMR (CDCl₃): 7.30 (s, 1H), 3.67 (m, 1H), 3.22 (s, 6H), 2.93 (s, 3H), 2.78 (s, 3H), 2.78 (s, 3H), 2.71 (s, 3H), 1.95 (m, 2H), 1.82 (m, 2H), 0.96 (t, 6H, J = 7.3 Hz).

Example 248

{5-Bromo-4-[8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazin-3-yl]-oxazol-2-yl}-dimethyl-amine Preparation of amine

A. 8-(1-ethyl-propyl)-2,6-dimethyl-3-oxazol-4-ylimidazo [1,2-b] pyridazine 599 mg 8-(1-ethyl-propyl)-3-oxo-2,6-dimethylimidazo [1,2-b] pyridazine (1.46 mmol), 622 mg oxazole (9.0 mmol), 79 mg triphenylphosphine (0.3 mmol) and 989 mg carboxylic acid Cesium (3.03 mmol) is placed in a reaction vial with 7 ml of dry DMF. N₂ gas is bubbled through the mixture for 30 minutes and 67 mg of Pd₂dba₃ (0.07 mmol) is added. The reaction vial is covered with a Teflon cap and stirred at 130 ° C. for 3 days. The reaction mixture is diluted with dichloromethane, washed with saturated NaCl, dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel chromatography column (hexane: EtOAc = 3: 1) to produce 172 mg (42%) of the title compound. Mass spectrum (m/e): 285. ¹H-NMR (CDCl₃): 8.04 (s, 1H), 7.97 (s, 1H), 6.78 (s, 1H), 3.35 (m, 1H), 2.80 (s, 3H), 2.65 (s, 3H), 1.86 (m, 4H), 0.88 (t, 6H). B. 3-(2,5-Dibromo-oxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethylimidazo [1,2-b] pyridazine. 172 mg 8-(1-ethyl-propyl)-2,6-dimethyl-3-oxazol-4-yl-imidazo [1,2-b] pyridazine (0.60 mmol) and 270 mg NBS (1.51 mmol) is dissolved in 8.0 ml dichloromethane and stirred overnight at room temperature. The reaction mixture is concentrated and applied onto a silica gel chromatography column (hexane: EtOAc = 3: 1) to yield 70 mg of the title compound (26%). Mass spectrum (m/e): 442; ¹H-NMR (CDCl₃): 6.82

(s, 1H), 3.32 (m, 1H), 2.59 (s, 3H), 2.54 (s, 3H), 1.86 (m, 4H), 0.89 (t, 6H, J = 7.4 Hz).

C. 5-Bromo-4-[(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-oxazol-2-yl-dimethyl-67 mg of 3-(2,5-dibromo-oxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.15 mmol) 146 mg of cesium carboxylate (0.45 mmol) and 3.0 ml of dimethylamine in 2.0 M THF (6 mmol) are placed in a 4 ml reaction vial and the vial is covered with a Teflon cap. The reaction vial is heated at 130 ° C. overnight. The reaction mixture is concentrated and applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1) to yield 53 mg of the title compound (87%). Mass spectrum (m / e): 406; ¹H-NMR (CDCl₃): 6.72 (s, 1H), 3.37 (m, 1H), 3.15 (s, 6H), 2.58 (s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J = 7.2 Hz).

Example 249

3-[3-chloro-4-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine
3-(4-Bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.20 g, 0. In a 49 mmol) flask, 0.5 g / mL Reike® Zn (1.3 mL, 0.97 mmol) is added. The slurry was heated at 55 ° C. for 1 hour, placed in a centrifuge for 5 minutes, and the solution was 5-bromo-1-methyl-¹H-[1,2,4] triazole (0.12 g, 0.73 mmol). And PdCl₂ (dppf) (0.018 g, 0.024 mmol). The solution is heated at 65 ° C. overnight, diluted with EtOAc (20 mL), washed with saturated NH₄Cl (15 mL), dried over MgSO₄, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-50% EtOAc gradient) to yield the title compound (0.018 g, 0.043 mmol, 9%). ¹H-NMR (CDCl₃): 5.0-6.7 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.95 (s, 3H), 5.72 (s, 1H), 7.62 (s, 1H), 8.01 (s, 1H). LC / MS (m / z): calcd [M + H]⁺: 415.2; ANALYSIS: 415.3.

Example 250

5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl-Preparation of dimethyl-amine
A. 8-(1-ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[1,2-b]pyridazine iodolimidazopyridazine (5.75 g, 19.7 mmol), triphenyl Phosphine (1.03 g, 3.94 mmol), Cs₂CO₃ (12.84 g, 39.4 mmol) and Pd₂(dba)₃ (900 mg, 0.98 mmol) were added to a shield tube with 65 mL of dry DMF. And N₂ gas is bubbled through the mixture for 5 minutes. Thiazol (8.36 g, 6.7 mL, 98.4 mmol) is added and the mixture is heated at 130 ° C. overnight. The mixture is cooled to room temperature and quenched by the addition of saturated NH₄Cl solution (200 mL). The mixture is extracted with Et₂O (3 × 100 mL) and the organic layer is washed with water (2 × 100 mL), saturated NaCl (100 mL), dried over MgSO₄ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent: hexane: EtOAc = 4: 1) to yield 3.80 g of the title compound (yield: 64%). ESIMS: m / z 301 [M + H]⁺.
B. 3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine CH₃CN at room temperature (55 mL. To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[1,2-b]pyridazine (3.80 g, 12.6 mmol) in NBS (5.18 g, 29.1 mmol) is added and the mixture is stirred at room temperature for 3 h. Filtration under vacuum forms a white ginger, yielding 4.86 g of the title compound (yield: 84%). ESIMS: m / z 459 [M + H]⁺.
C. 3-(4-Bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine 3-(3) in THF (150 mL). Of 2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (4.86 g, 10.6 mmol) To the solution, BuLi (6.53 mL, 1.6M in hexane, 10.6 mmol) in hexane is added dropwise at -78 ° C. under N₂ atmosphere for 10 minutes. The mixture is stirred at -78 ° C. for 30 minutes. Water is added and the mixture is extracted with Et₂O (3 × 100 mL), dried over MgSO₄ and concentrated in vacuo. The crude product is purified by flash chromatography on silica gel (eluent: hexane: EtOAc 5: 1) to yield 3.28 g of the title compound (yield: 82%). ESIMS: m / z 379 [M + H]⁺ (of 381).
D. NMP of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[1,2-b]pyridazine shield tube 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (2.45 g) in 35 mL. To a solution of 6.5 mmol) is added FSO₂CF₂CO₂Me (2.5 g, 1.65 mL, 13 mmol) and CuI (2.48 g, 13 mmol). N₂ gas is bubbled through the mixture for 5 minutes and the mixture is heated at 120 ° C. for 9 hours. After cooling to room temperature, water (100 mL) and saturated NaCl solution (100 mL) are added to the mixture. The mixture is extracted with Et₂O (5 × 80 mL), washed with water (2 × 100 mL), dried over MgSO₄ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent: hexane: EtOAc 5: 1) to yield 960 mg of the title compound (yield: 40%). ESIMS: m / z 369 [M + H]⁺.
E. 3-(2-Bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine N₂ atmosphere 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[1,2-b]pyridazine in 40 mL of THF under To a solution of (915 mg, 2.48 mmol) BuLi (1.56 mL, 1.6 M in hexane, 2.98 mmol) at -78 ° C. is slowly added. The mixture is stirred at -78 ° C. for 30 minutes. Then a solution of CBr₄ (989 mg, 2.98 mmol) in 3 mL of THF is added and the mixture is stirred at -78 ° C. for 45 minutes. The reaction is quenched with the addition of saturated NH₄Cl solution (50 mL), extracted with Et₂O (2 × 50 mL), dried over MgSO₄ and concentrated in vacuo. The crude product is purified by flash chromatography on silica gel (eluent: CH₂Cl₂) to yield 685 mg of the title compound (yield: 62%). ¹H-NMR (CDCl₃): 5.0-6.6 (t, J = 7.5 Hz, 6H), 1.82 (m, 4H), 2.45 (s, 3H), 2.51 (s, 3H), 3.27 (m, 1H), 6.74 (s, 1H). ESIMS: m / z 447, 449 [M + H]⁺.
F. 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl-Dimethyl-amine 100 mg 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (0.22 mmol) and 218 mg cesium carboxylate (0.66 mmol) in a 4 ml reaction vial and add 3 ml of 2M dimethylamine in THF. The reaction vial is covered with a Teflon cap and heated at 120 ° C. overnight. The reaction mixture is filtered, concentrated and applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1) to yield 95 mg of the title compound. Yield 94%. Mass spectrum (m / e): 412 (M + 1).

Example 251

8-(1-Ethyl-propyl)-2,6-dimethyl-3-[2-(2-methyl-2H-[1,2,4] triazol-3-yl)-4-trifluoromethyl-Preparation of thiazol-5-yl]-imidazo[1,2-b]pyridazine
164 mg of 1-methyl-1,2,4-triazole (1.96 mmol) is dissolved in 2 mL of THF and cooled to -78 ° C. 0.8 mL of 2.5M n-butyllithium in hexane (1.96 mmol) is added slowly, stirred at -78 ° C., warmed to room temperature, stirred at room temperature for 15 minutes and cooled to -78 ° C.. Add 3.96 mL of 0.5 M ZnCl₂ in THF (1.98 mmol) and stir at room temperature for 15 minutes. 180 mg of 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine and 54 mg of PdCl₂(pddf) (0.06 mmol) is added. The vial is covered with a Teflon cap and heated at 80 ° C. overnight. NH₄Cl water is added to quench the reaction, the mixture is extracted with CH₂Cl₂, dried over Na₂SO₄ and evaporated. The crude product is applied onto a silica gel chromatography column (hexane: AcOEt = 3: 1) to produce 119 mg of the title compound. Yield 58%. Mass spectrum (m / e): 449 (M + 1).

Example 252

Preparation of 8-(1-ethyl-propyl)-6-methyl-3-(3-methyl-thiophen-2-yl)-2-trifluoromethyl-imidazo[1,2-b]pyridazine
A. 8-(1-Ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[1,2-b]pyridazine α-bromotrifluoroacetone (402 mg, 2.93 mmol) was added to EtOH (2.0 mL). Add to a dry 10 mL microwave reaction tube containing 4-(1-ethyl-propyl)-6-methyl-pyridazin-3-ylamine (500 mg, 2.79 mmol). The resulting mixture is heated in the microwave at 110 ° C. for 1 hour. NaHCO₃ (246.5 mg, 2.93 mmol) is added and the reaction is mixed well for 5 minutes. The reaction is then heated in the microwave at 110 ° C. for 1 hour. The solvent is removed at reduced pressure and the reaction is diluted with ethyl acetate (30 mL). The organic layer is washed with H₂O (3 × 10 mL) and the combined aqueous layer is extracted with ethyl acetate (2 × 20 mL). The combined organic extracts are dried over Na₂SO₄, filtered and purified by silica gel chromatography to yield the title compound (29.5 mg, 0.068 mmol, 9.8%). ¹H-NMR (CDCl₃): 5.0-6.7 (t, J = 7.5 Hz, 6H), 1.85 (m, 4H), 2.60 (s, 3H), 3.30 (m, 1H), 6.80 (s, 1H), 8.14 (s, 1H) ppm.

ES-MS (m/z): calcd (M + H)⁺: 271.29; analysis: 272.2

B. 8-(1-ethyl-propyl)-6-methyl-3-(3-methyl-thiophen-2-yl)-2-trifluoromethyl-imidazo [1,2-b] pyridazine 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo [1,2-b] pyridazine (300 mg, 1.11 mmol), 2-bromo-3-methyl-thiophene (216 mg, 1.22 mmol) and Cs₂CO₃ (1.7 ml) is added to a dry 10 ml round bottom flask with a reflux condenser containing 5 (760 mg, 2.33 mmol). The mixture is degassed with N₂ bubbling for 15 minutes and Pd₂(dba)₃ (50.8 mg, 0.055 mmol) and PPh₃ (58.2 mg, 0.222 mmol) are added. The reaction mixture is stirred at 130 °C overnight. The mixture is cooled to room temperature, diluted with H₂O and extracted with EtOAc (3 × 20 ml). The organic layer is dried (Na₂SO₄), filtered and clarified by HPLC to yield the title compound (32 mg, 0.067 mmol, 8%). ¹H-NMR (CDCl₃), δ 0.93 (t, J = 7.2 Hz, 6H), 1.91 (m, 4H), 2.15 (s, 3H), 2.58 (s, 3H), 3.36 (m, 1H), 6.91 (s, 1H), 7.08 (d, J = 5.3 Hz, 1H), 7.55 (d, J = 5.5 Hz, 1H) ppm. ES-MS (m/z): calcd (M + H)⁺: 367.44; analysis: 368.1.

Example 253

3-(3-Chloro-5-(2-methyl-2H-[1,2,4] triazol-3-yl)-thiophen-2-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo [1,2-b] pyridazine preparation
8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo [1,2-b] pyridazine (182 mg, 0.671 mmol), 5-(5) in a dry 25 mL round bottom flask, 2-bromo-4-chloro-thiophen-2-yl-1-methyl-1,2,4-triazoles of 1 H-[1,2,4]-Le (225 mg, 0.805 mmol), KOAc (330.2 mg, 3.36 mmol) and TBAB (217 mg, 0.671 mmol) are dissolved in NMP (3 mL). The mixture is degassed with nitrogen bubbling. Then Pd(OAc)₂ (8 mg, 0.034 mmol) and TDBPP (20.4 g, 0.34 moles) are added. The reaction mixture is heated at 125 °C for 3 hours to produce the title compound (125 mg, 0.267 mmol, 40%). ¹H-NMR (CDCl₃), δ 0.88 (t, J = 7.2 Hz, 6H), 1.87 (m, 4H), 2.587 (s, 3H), 3.32 (m, 1H), 4.16 (s, 3H), 6.86 (s, 1H), 7.51 (s, 1H), 7.91 (s, 1H) ppm. ES-MS (m/z): calcd (M + H)⁺: 468.93; analysis: 469.2.

Example 254

3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo [1,2-b] Preparation of pyridazine
A. 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo [1,2-b] pyridazine. 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo [1,2-b] pyridazine (460 mg, 1.70 mmol) in a dry 25 mL round bottom flask was added to dry THF (3.5 mL) and cool to -78 °C. A solution of 2.5 M n-butyllithium in hexane (748 μL, 1.87 mmol) is added dropwise. The reaction mixture is stirred at -78 °C for 20 minutes and heated at 0 °C for 15 minutes. A solution of t2 (463 mg, 1.79 mol) in THF (2.0 mL) is added dropwise. The reaction is stirred at 0 °C for 15 minutes and then heated to room temperature. The reaction is stirred overnight and the solvent is removed at reduced pressure. The reaction mixture is redissolved in ethyl acetate (50 mL) and washed with a 1N solution of Na₂S₂O₃ (2 × 20 mL). Extract the aqueous layer with ethyl acetate (2 × 40 mL). The combined organic extract is dried over Na₂SO₄, filtered and purified via silica gel chromatography to yield the title compound (595 mg, 1.50 mmol, 88%). ¹H-NMR (CDCl₃), δ 0.82 (t, J = 8.0 Hz, 6H), 1.83 (m, 4H), 2.64 (s, 3H), 3.27 (m, 1H), 6.82 (s, 1H) ppm. ES-MS (m/z): calcd (M + H)⁺: 397.18; analysis: 398.3.
B. 2,4-Dichloro-thiazole. In a 250 mL round bottom flask, 2,4-thiazolidinedione (12.5 g, 107 mmol) is dissolved in phosphonic acid oxychloride (70 mL) and pyridine (8.5 mL). The mixture is stirred under reflux for 3 hours and cooled to room temperature. The reaction mixture is slowly poured into ice water and extracted with dichloromethane. The combined organic extract is dried over Na₂SO₄, filtered and concentrated. The residue is purified via silica gel chromatography to yield the title compound (9.18 g, 59.6 mmol, 56%). ¹H-NMR (CDCl₃), δ 7.01 (s, 1H) ppm.
C. 4-(4-Chloro-thiazol-2-yl)-mol hoin. In a 75 mL dry pressure vessel, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and morpholine (560 μL, 6.4 mmol) are dissolved in dry THF (2.0 mL). Cs₂CO₃ (1.56 g, 4.8 mmol) is added and the reactor is sealed. The reaction mixture is heated at 110 °C overnight. The solvent is removed at reduced pressure and the crude reaction mixture is purified via silica gel chromatography to yield the title compound (597 mg, 2.92 mmol, 91%). ¹H-NMR (CDCl₃), δ 3.45 (m, 4H), 3.79 (m, 4H), 6.31 (s, 1H) ppm. ES-MS (m/z): Calcd (M + H)⁺: 204.68; analysis: 205.2.
D. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo [1,2-b] pyridazine. In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo [1,2-b] pyridazine (250 mg, 0.630 mmol), 4-(4-Chloro-thiazol-2-yl)-mol hoin (194 mg, 0.945 mmol) and Cs₂CO₃ (410 mg, 1.26 mmol) are dissolved in DMF. The mixture is degassed with nitrogen bubbling for 15 minutes. Then Pd₂(dba)₃ (18 mg, 0.032 mmol) and PPh₃ (93 mg, 0.126 mmol) are added. The reaction mixture is heated at 130 °C overnight. Cool the reaction to room temperature, quench with saturated NH₄Cl solution (20 mL), and extract with Et₂O (3 × 50 mL). The combined organic extract is washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified via reverse phase HPLC with a 30-80% gradient of CH₃CN in 10 mM NH₄HCO₃ / H₂O / 5% CH₃CN (pH 10.0) to give the title compound (11 mg, 0.023 mmol, 4%). ¹H-NMR (CDCl₃), δ 0.86 (t, J = 7.3 Hz, 6H), 1.84 (m, 4H), 2.55 (s, 3H), 3.31 (m, 1H), 3.54 (dd, J = 5.2, 4H), 3.84 (dd, J = 5.2 Hz, 4H), 6.82 (s, 1H) ppm. ES-MS (m/z): calcd (M + H)⁺: 473.95; analysis: 474.2.

Example 255

{4-Chloro-5-[8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl}-Dimethyl-amine preparation
A. (4-Chloro-thiazol-2-yl)-dimethyl-amine Using a procedure analogous to Example 254C, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and dimethylamine (2 in THF A 0.0 M solution, 3 mL, 6.4 mmol) is reacted to produce the title compound (59 mg, 0.192 mmol, 15%). ¹H-NMR (CDCl₃), δ 3.09 (s, 6H), 6.22 (s, 1H) ppm. ES-MS (m/z): Calcd (M + H)⁺: 162.64; analysis: 163.2.
B. (4-Chloro-5-[8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo [1,2-b] pyridazin-3-yl]-thiazol-2-yl)-Dimethyl-amine Using a procedure analogous to Example 254D, 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo [1,2-b] pyridazine (250 mg, 0.630 mmol) is mixed with (4-chloro-thiazol-2-yl)-dimethyl-amine (154 mg, 0.945 mmol) to produce the required product. ¹H-NMR (CDCl₃), δ 0.85 (t, J = 7.4 Hz, 6H), 1.83 (m, 4H), 2.55 (s, 3H), 3.16 (s, 6H), 3.31 (m, 1H), 6.81 (s, 1H) ppm. ES-MS (m/z): calcd (M + H)⁺: 431.91; analysis: 432.2.

Example A

In vivo efficacy assessment using in vitro binding To assess in vivo efficacy, the compounds of the invention are evaluated using in vitro binding. D. R. Gehlert et al., EJP 509: 145-153 (2005), the compound is administered orally to rats. The binding of [¹²⁵I]-saubagin to the cerebellum was then determined according to Gehlert et al. In vitro evaluation as described in. For example, Example 199 gives an ED₅₀ result of 1.3 mg/kg.

Example B

CRF1 filtration binding experiments The restriction of the plasmid-based human CRF1 expression in generating recombinant cell lines with sufficient receptor density to develop binding experiments is the limitation of the Phoenix Retrovirus approved by Stanford. Overcoming using expression systems. A stable HEK-hCRF1 cell line was

used to prepare the membrane, and the binding reaction (200 μ l) was performed as 50 μ l of ^{125} I-saubagin (final 0.2 nM), 50 μ l compound and 100 μ l CRF1 membrane (25 μ g / reactant). It was. The reaction is warmed at room temperature for 2 hours and then terminated by filtration through a pre-treated F8 Millipore glass fiber filter plate (96 well). Plates were washed twice with ice cold assay buffer (50 mM Tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried until morning, MicroBeta Count with 100 μ l Microscint 40 of the counter. Non-specific binding (NSB) is determined in the presence of 0.5 μ M unlabeled subagin. Typically determined in triplicate, the median data points are plotted by Graph Pad Prism. Using this analysis, the claimed specific compounds of the invention inhibit the binding of ^{125} I-saubagin (4 nM) to roller / adherent cells with K_i (inhibition constant) below 1 μ M. For example, Examples 102 and 199 exhibit K_i of 4.92 ± 0.57 nM and 9.98 ± 0.72 nM, respectively.

Example C

CRF2 filtration binding experiments The restriction of plasmid-based human CRF2 expression in generating recombinant cell lines with sufficient receptor density to develop binding experiments is the limitation of the Phoenix Retrovirus licensed from Stanford. Overcoming using expression systems. A stable HEK-hCRF2 cell line is used to prepare the membrane and the binding reaction (200 μ l) is performed as 50 μ l of ^{125} I-saubagin (0.2 nM final concentration), 50 μ l compound and 100 μ l CRF2 membrane (25 μ g / reaction). The reaction is warmed at room temperature for 2 hours and then terminated by filtration through a pre-treated F8 Millipore glass fiber filter plate (96 well). Plates were washed twice with ice cold assay buffer (50 mM Tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air-dried until morning, and a MicroBeta counter Count with 100 μ l Microscint 40. Non-specific binding (NSB) is determined in the presence of 0.5 μ M unlabeled subagin. Alternatively, compounds are evaluated using scintillation proximity analysis. This analysis consists of 50 μ l of ^{125} I-saubagin (0.2 nM final concentration), 50 μ l of compound or unlabeled subagin (NSB), and 100 μ l containing 250 μ g wheat germ agglutinin (WGA) SPA bead (1.5 μ g / Reaction). The plate is warmed at room temperature for 4-5 hours and then centrifuged at 200 $\times$ g for 10 minutes. Bound radioactivity is assessed using a Wallac TriLux scintillation counter. Binding is typically assessed using triplicate determinations and median data points plotted by Graph Pad Prism. Compounds are first screened by fixed concentration, and when sufficient activity is observed, a concentration response curve is generated. The compounds of the invention exhibit the weak affinity of the CRF2 receptor when tested in CRF2 binding experiments. For example, Examples 102 and 199 exhibit a rate of 9.0 ± 2.6 and 16.9 ± 1.9 at 50 μ M, respectively. These results suggest that the compounds of the present invention are very selective for the CRF1 receptor.

Example D

Bioavailability and Pharmacokinetic Analysis Properties The compounds of formula I are antagonists of CRF1 and have surprisingly useful properties related to their pharmacokinetics and bioavailability. The distribution amount (Vdist) correlates the dose in the living body with the drug concentration in blood or plasma. The distribution amount is the amount of liquid necessary to contain the total amount of drug in the body at the same concentration as in blood or plasma. $V_{dist} = \text{in vivo drug dose} / \text{drug concentration in blood or plasma}$ (Goodman and Gilman's). For a dose of 10 mg and a plasma concentration of 10 mg / L, the dispensed volume is 1 liter. The distribution amount reflects the extent to which the drug is present in extravascular tissue. The large partition volume reflects the tendency of the compound to bind to tissue components compared to plasma protein binding. In a clinical setting, Vdist can be used to determine whether the initial loading has made a steady state concentration. To test the dose, Male Sprague Dawley rats (N = 3) received a single intravenous dose of 3 mg / kg of compound. Multiple plasma samples are collected 0.08 to 24 hours after dosing. Plasma samples are analyzed by LC / MS / MS to determine plasma concentration enrichment. Plasma pharmacokinetic calculations are performed to determine pharmacokinetic parameters including Vdist and plasma clearance (Clp). The overwhelming majority of common CNS and cardiovascular drugs exhibit human Vdist of less than 10 L / Kg. CRF antagonist CP154526 (Schultz et al., Proc. Natl. Acad. Sci. (USA), 93: 10477 (1996)) and NBI30775 (Chen et al., Drug) presenting rat Vdist of 114 L / Kg and 76 L / Kg. Compared to each of Development Research, 65: 216 (2005)), after single intravenous administration, thiazole Examples 48 and 199 of the present invention exhibit only 9 and 2 L / Kg of rat Vdist. Furthermore, thiophene Examples 88 and 99 of the present invention exhibit rat Vdist of only 44 and 17 L / kg, respectively.

Patent Citations (7)

Publication number	Priority date	Publication date	Assignee	Title
JP2000033561A *	1996-02-07	2000-03-28	ジヤンセン・フアーマシユーチカ・ナームローゼ・フエンノートシャツプ	Pyrazolopyrimidines as CRF receptor antagonists
WO2002016363A1 *	2000-07-17	2002-02-28	Merck Sharp & Dohme Limited	Imidazolophthalazine derivatives as ligands for gabaa receptors
WO0002962800A1 *	2001-02-08	2002-08-15	Eisai Co., Ltd.	Bicyclic nitrogenous fused-ring compound
JP2003025291A *	2000-03-01	2003-08-26	ジヤンセン・フアーマシユーチカ・ナームローゼ・フエンノートシャツプ	2,4-disubstituted thiazolyl derivatives
JP200313176A *	2002-04-24	2003-11-06	Sankyo Co Ltd	Aminoazole derivative
JP2005325127A *	2002-01-18	2005-11-24	Sumitomo Chemical Takeda Agro Co Ltd	Imidazopyridazine derivative
Family To Family Citations				
TW327462B *	2002-01-18	2010-07-21	Sumitomo Chemical Co	Condensed heterocyclic sulfonyl urea compound, a herbicide containing the same, and a method for weed control using the same

* Cited by examiner, † Cited by third party

Cited By (50)

Publication number	Priority date	Publication date	Assignee	Title
JP201309375A *	2009-10-30	2013-03-14	ジヤンセン・フアーマシユーチカ・ナームローゼ・フエンノートシャツプ	Imidazo [1,2-b] pyridazine derivatives and their use as PDE10 inhibitors

JP201527295A *	2014-05-30	2015-12-17	東ソー株式会社	Production method of dithienobenzodithiophene
JP2017014240A *	2009-10-26	2017-01-19	シグナル ファーマシューティカルズ, エルエルシー	Methods of synthesis and purification of heteroaryl compounds
JP2020530832A *	2017-08-14	2020-10-29	スブルース バイオサイエンス イン コーポレイテッド	Corticotropin-releasing factor receptor antagonist
Family To Family Citations				
US772336B2	2005-09-22	2010-05-25	Bristol-Myers Squibb Company	Fused heterocyclic compounds useful as kinase modulators
SI2044025T1	2006-05-30	2013-01-31	Novartis Ag	Quinolone derivatives and their pharmaceutical compositions
ES2428543T3 *	2006-09-20	2013-11-08	Eli Lilly And Company	Thiophenepyrzolo[pyrimidine] Compounds
EA20100123A1	2007-07-26	2010-08-30	Новаарт Аг	ORGANIC COMPOUNDS
EP2235319A1 *	2007-12-21	2010-10-06	Wyeth LLC	Imidazo [1,2-b] pyridazine compounds as modulators of liver x receptors
WO2009094224A1	2008-01-25	2009-07-30	Millennium Pharmaceuticals, Inc.	Thiophenes and their use as phosphatidylinositol 3-kinase (pi3k) inhibitors
WO2009100375A1	2008-02-06	2009-08-13	Bristol-Myers Squibb Company	Substituted imidazopyridazines useful as kinase inhibitors
SI2350675T1	2008-09-22	2014-06-30	Array Biopharma, Inc.	Substituted imidazo[5,1,2b]pyridazine compounds as trk kinase inhibitors
KR102007619B1	2008-10-22	2019-10-28	에스티 바이오파마 인크.	SUBSTITUTED PYRAZOLO[1,5-a]PYRIMIDINE COMPOUNDS AS TRK KINASE INHIBITORS
US8796314B2	2009-01-30	2014-08-05	Millennium Pharmaceuticals, Inc.	Heteroaryls and uses thereof
US9090601B2	2009-01-30	2015-07-28	Millennium Pharmaceuticals, Inc.	Thiazole derivatives
EP2391619A1 *	2009-01-30	2011-12-07	Millennium Pharmaceuticals, Inc.	Heteroaryls and their use as pi3k inhibitors
AR077468A1	2009-07-09	2011-08-31	Array Biopharma Inc	PIRAZOLO COMPOUNDS (1,5-A) PYRIMIDINE SUBSTITUTED AS TRK-QUINASA INHIBITORS
AR080754A1	2010-03-09	2012-05-09	Janssen Pharmaceutica Nv	IMIDAZO DERIVATIVES (1,2-A) PIRAZINA AND ITS USE AS PDE10 INHIBITORS
CN101830909A *	2010-04-26	2010-09-15	西安近代化学研究所	Preparation method of tetrahydro-cyclopentyl[2,1-b,3,4-b'] bi-thiophene ketone
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US8859758B2	2010-08-11	2014-10-14	Millennium Pharmaceuticals, Inc.	Heteroaryls and uses thereof
JP2013542941A	2010-10-13	2013-11-28	ミレニアム ファーマシューティカルズ, インコーポレイテッド	Heteroaryl and uses thereof
DE102011075396A1 *	2011-05-06	2012-11-08	Bayer Pharma Aktiengesellschaft	Substituted imidazopyridazines and their use
AU2012277912B2	2011-06-27	2017-03-23	Janssen Pharmaceutica Nv	1-aryl-4-methyl-1,2,4-triazolo[4,3-a]quinoxaline derivatives
WO2013064445A1 *	2011-11-01	2013-05-10	F. Hoffmann-La Roche Ag	Imidazopyridazine compounds
ES2855575T3	2012-06-26	2021-09-23	Janssen Pharmaceutica Nv	Combinations comprising 4-methyl- [1,2,4] triazolo [4,3-a] quinoxaline compounds as PDE2 inhibitors and PDE10 inhibitors for use in the treatment of neurological or metabolic disorders
WO2014099305A1	2012-07-09	2014-01-16	Janssen Pharmaceutica Nv	Inhibitors of phosphodiesterase 10 enzyme
WO2014058249A1	2012-12-19	2014-06-26	Basf Se	Fungicidal imidazolyl and triazolyl compounds
EP2746255A1	2012-12-19	2014-06-25	Basf Se	Substituted [1,2,4]triazole and imidazole compounds
EP2746277A1	2012-12-19	2014-06-25	Basf Se	Fungicidal imidazolyl and triazolyl compounds
WO2014096381A1	2012-12-19	2014-06-26	Basf Se	Fungicidal imidazolyl and triazolyl compounds
EP2746279A1	2012-12-19	2014-06-25	Basf Se	Fungicidal imidazolyl and triazolyl compounds

EP2746255A1	2012-12-19	2014-06-25	Basf Se	Fungicidal imidazolyl and triazolyl compounds
EP2746264A1	2012-12-19	2014-06-25	Basf Se	Substituted [1,2,4]triazole and imidazole compounds
EP2746260A1	2012-12-21	2014-06-25	Basf Se	Substituted [1,2,4]triazole and imidazole compounds
EP2746259A1	2012-12-21	2014-06-25	Basf Se	Substituted [1,2,4]triazole and imidazole compounds
EP2746257A1	2012-12-21	2014-06-25	Basf Se	Substituted [1,2,4]triazole and imidazole compounds
EP2746258A1	2012-12-21	2014-06-25	Basf Se	Substituted [1,2,4]triazole and imidazole compounds
CN103058933B *	2012-12-29	2015-06-17	泉州师范学院	Method for industrial preparation of 6-methyl-3-aminopyridazine
RU2020112197A	2014-01-21	2020-05-21	Ньюоркрайн Байосайенсиз, Инк.	CFR1 receptor antagonists for the treatment of congenital adrenal cortex hyperplasia
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US10045991B2	2016-04-04	2018-08-14	Lexo Oncology, Inc.	Methods of treating pediatric cancers
AU2017246554B2	2016-04-04	2022-06-18	Lexo Oncology, Inc.	Liquid formulations of (S)-N-(S-(R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide
RS61463B1	2016-05-18	2021-03-31	Lexo Oncology Inc	Preparation of (s)-n-(5-(r)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide
US10665927B2 *	2016-09-16	2020-06-02	Helmholtz Zentrum Muenchen—Deutsches Forschungszentrum Für Gesundheit Und Umwelt (GmbH)	TRAF 6 inhibitors
JOP20190092A1	2016-10-26	2019-04-25	Array Biopharma Inc	PROCESS FOR THE PREPARATION OF PYRAZOLO[1,5-a]PYRIMIDINES AND SALTS THEREOF
JOP20190213A1	2017-03-16	2019-09-16	Array Biopharma Inc	Macrocyclic compounds as rosl kinase inhibitors

* Cited by examiner, † Cited by third party, ‡ Family to family citation

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JP4971360B2	2012-07-11	Imidazopyridazine compounds
AU2017362350B2	2021-12-23	Pyrolopyrimidines as CFTR potentiators
JP4801724B2	2011-10-26	Acetylenyl-pyrazolo-pyrimidine derivatives as mGluR2 antagonists
TW547226B	2019-01-11	Novel (hetero)aryl substituted piperidinyl derivative, preparation method thereof and pharmaceutical composition containing the same
DE60214592T2	2007-04-12	Imidazopyrimidine Derivatives as Ligands for GABA Receptors
US7557103B2	2009-07-07	Imidazopyridazine compounds
JP5608899B2	2015-03-25	Benzimidazole inhibitors produced by leukotrienes
TW200410851A	2004-10-01	Pyrolopyridazine derivatives
JP6305515B2	2018-04-04	Acyclic cyanoethylpyrazolopyridone as a Janus kinase inhibitor
US20100356527A1	2010-03-04	Benzofuran compounds useful in the treatment of conditions mediated by the action of pge2 at the ep1 receptor
US8957668B1	2002-05-28	Tetrahydroindolone derivatives as gabaaalpha5 ligands for enhancing cognition
WO2019089670A1	2019-05-09	Alkene compounds as farnesoid x receptor modulators
JP2021515773A	2021-06-24	Aminopyrazine diol compound as a PI3K-γ inhibitor
US20040058970A1	2004-03-25	Cognition enhancing derivatives of isoxazole triazoloindane GABA-A alpha 5 receptor subunit ligands

Priority And Related Applications

Applications Claiming Priority (3)

Application	Filing date	Title
US6638160P	2005-03-21	
US60/663,816	2005-03-21	
PG1/US2006/009942	2006-03-20	Imidazopyridazine compounds

Legal Events

Date	Code	Title	Description
2009-03-14	A621	Written request for application examination	Free format text: JAPANESE INTERMEDIATE CODE: A621 Effective date: 20090313
2009-03-26	RD03	Notification of appointment of power of attorney	Free format text: JAPANESE INTERMEDIATE CODE: A7423 Effective date: 20090325
2009-09-18	RD04	Notification of resignation of power of attorney	Free format text: JAPANESE INTERMEDIATE CODE: A7424 Effective date: 20090917
2012-03-15	TRDD	Decision of grant or rejection written	
2012-03-22	A01	Written decision to grant a patent or to grant a registration (utility model)	Free format text: JAPANESE INTERMEDIATE CODE: A01 Effective date: 20120321
2012-03-29	A01	Written decision to grant a patent or to grant a registration (utility model)	Free format text: JAPANESE INTERMEDIATE CODE: A01
2012-04-12	A61	First payment of annual fees (during grant procedure)	Free format text: JAPANESE INTERMEDIATE CODE: A61 Effective date: 20120405
2012-04-13	FPAY	Renewal fee payment (event date is renewal date of database)	Free format text: PAYMENT UNTIL: 20150413 Year of fee payment: 3
2012-04-13	R150	Certificate of patent or registration of utility model	Free format text: JAPANESE INTERMEDIATE CODE: R150
2015-03-31	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2016-04-13	LAPS	Cancellation because of no payment of annual fees	

Concepts

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Name	Image	Sections	Count	Query match
imidazopyridazines		title	1	0.000
compounds		claims,abstract,description	348	0.000
disease		claims,abstract,description	25	0.000
pharmaceutical composition		claims,abstract,description	8	0.000
methoxy, dimethylamino		claims,description	186	0.000
ethanol		claims,description	52	0.000
hydrogen		claims,description	52	0.000
hydrogen		claims,description	51	0.000
methyl group		claims,description	47	0.000
sodium chloride		claims,description	28	0.000

ethyl group	claims,description	22	0.000
salts	claims,description	19	0.000
drug	claims,description	17	0.000
hydrogen atoms	claims,description	15	0.000
Anxiety disease	claims,description	12	0.000
Mammalia	claims,description	12	0.000
hydrogen	claims,description	12	0.000
drug carrier	claims,description	7	0.000
alkyl group	claims,description	6	0.000
methoxy group	claims,description	6	0.000
phenyl group	claims,description	6	0.000
trifluoromethyl group	claims,description	6	0.000
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Irritable Bowel Syndrome	claims,description	5	0.000
anxiety	claims,description	5	0.000
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Major depression	claims,description	4	0.000
aluminum nitride	claims,description	4	0.000
cyano group	claims,description	4	0.000
diluting agent	claims,description	4	0.000
hydroxy functional group	claims,description	4	0.000
manufacturing process	claims,description	4	0.000
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(C1-C2) alkyl group	claims,description	3	0.000
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tert-butyl group	claims,description	3	0.000
(C1-C3) alkyl group	claims,description	2	0.000
(C3-C5) cycloalkyl group	claims,description	2	0.000
Drug withdrawal syndrome	claims,description	2	0.000
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carbamoyl group	claims,description	2	0.000
ethynyl group	claims,description	2	0.000
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n-propyl group	claims,description	2	0.000
sulfur	claims,description	2	0.000
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halogen functional group	claims	9	0.000
alkyl sulfonyl group	claims	1	0.000

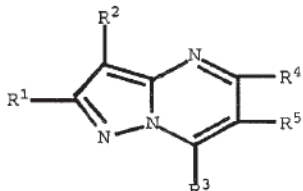
⌘ pharmaceutical preparation	claims	1	0.000
⌘ crf1	abstract,description	19	0.000
⌘ receptor antagonist	abstract,description	5	0.000
⌘ imidazo[1,2-b]pyridazines	abstract,description	2	0.000
⌘ therapeutic procedure	abstract,description	2	0.000
⌘ Mental disease	abstract	1	0.000
⌘ neurological	abstract	1	0.000
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 487/04, A61K 31/519, A61P 25/00		A2	(11) International Publication Number: WO 00/59908
			(43) International Publication Date: 12 October 2000 (12.10.00)
(21) International Application Number: PCT/US00/09111 (22) International Filing Date: 6 April 2000 (06.04.00) (30) Priority Data: 60/128,006 6 April 1999 (06.04.99) US (71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; Chestnut Run Plaza, 974 Centre Road, Wilming- ton, DE 19807 (US). (72) Inventors: GILLIGAN, Paul, J.; 2629 Pennington Drive, Wilmington, DE 19810 (US). WILDE, Richard, G.; 205 Roseman Court, Newark, DE 19711 (US). (74) Agent: RUBIN, Kenneth, B.; Du Pont Pharmaceuticals Com- pany, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).			(81) Designated States: AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, VN, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PYRAZOLOPYRIMIDINES AS CRF ANTAGONISTS <div style="text-align: center;">  <p>(I)</p> </div>			
(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

5 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, 10 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 15 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 20 and colonic hypersensitivity associated with psychopathological disturbance and stress.

BACKGROUND OF THE INVENTION

 Corticotropin releasing factor (herein referred to 25 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 30 (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, 35 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 α -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)].

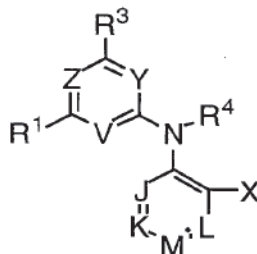
Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton 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 (α -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:

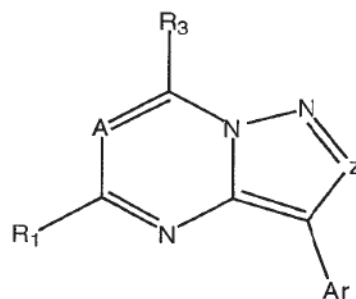


and their use to treat psychiatric disorders and neurological diseases. Included in the description are fused pyridines and pyrimidines of the formula:

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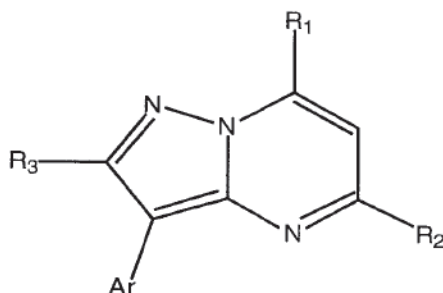
where: V is CR^{1a} or N; Z is CR² or N; A is CR³⁰ or N; and D is CR²⁸ or N.

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



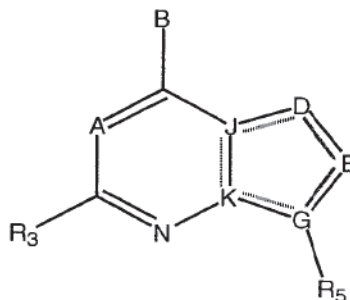
wherein z is N or CR² and A is N or CR.

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



wherein Ar is phenyl, pyridyl and substituted versions
15 thereof.

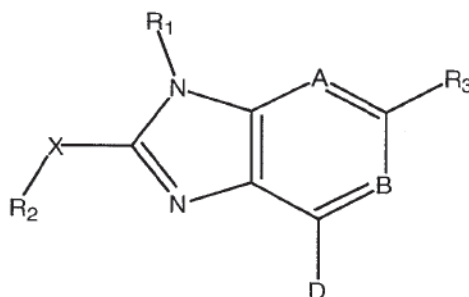
WO 98/08847, published March 5, 1998, discloses CRF antagonist compounds of the formula:



6

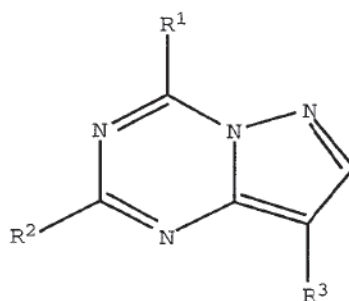
wherein B is selected from a variety of non-aryl groups and R⁵ is selected from certain groups such as phenyl or pyridyl or substituted versions thereof.

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



wherein D is an aryl or heteroaryl group and R¹ is selected from certain non-aryl or non-heteroaryl groups.

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



15 where R¹ is OH or alkanoyl, R² is H, OH, or SH, and R³ 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.

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

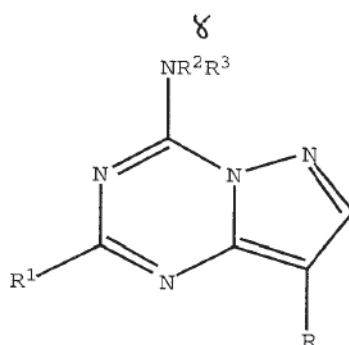
where A is CH or N, R⁰ and R³ are H or alkyl, and R¹ and R² are H, alkyl, alkoxyl, alkylthio, nitro, etc., and
5 states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and prostatic carcinoma.

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

10

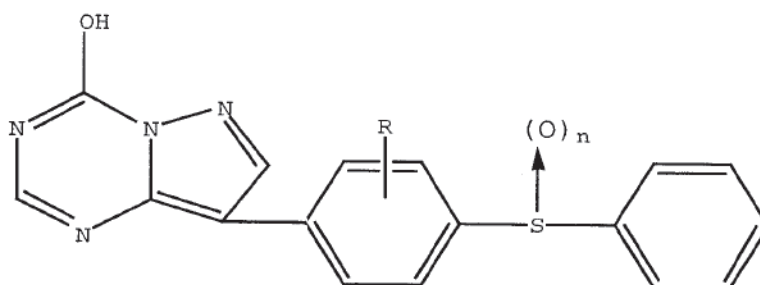
where R₁ is CH₃, C₂H₅ or C₆H₅, X is H, C₆H₅, m-CH₃C₆H₄, CN, COOEt, Cl, I or Br, Y is H, C₆H₅, o-CH₃C₆H₄, or p-CH₃C₆H₄,
15 and Z is OH, H, CH₃, C₂H₅, C₆H₅, n-C₃H₇, i-C₃H₇, SH, SCH₃, NHC₄H₉, or N(C₂H₅)₂, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

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



where R¹ is H or alkyl, R² is H or alkyl, R³ is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is
 5 pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

US 5,137,887 discloses pyrazolotriazines of the formula



10

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

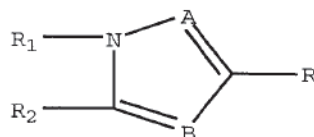
15 US 4,892,576 discloses pyrazolotriazines of the formula

20 where X is O or S, Ar is a phenyl, naphthyl, pyridyl or thienyl group, R₆-R₈ are H, alkyl, etc., and R₉ is H,

9

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
5 compound of the formula



where A can be N, B can be CR₃, R₃ can be phenyl or
10 substituted phenyl, etc., R is -N(R₄)SO₂R₅ or -SO₂N(R₆)R₇
and R₁ and R₂ can be taken together to form

15 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

20

where Z is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇, iso-C₃H₇, SH, SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, R is H or CH₃, and R₁ is CH₃
25 or C₂H₅. 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

5

where Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, R¹ is H, alkyl, etc., R² is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, R³ is H, alkyl or phenyl, R⁴ is H, alkyl, alkoxy carbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R⁵ and R⁶ are H or alkyl.

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

20 where R₁, R₂, R₃ and R₄ are H, carboxyl, alkoxy carbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R₅ is SR₆ or NR₇R₈, R₆ is pyridyl or optionally substituted phenyl, and R₇ and R₈ are H or optionally substituted phenyl.

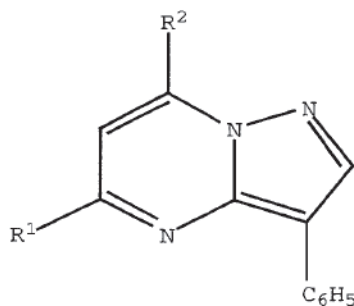
II

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

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

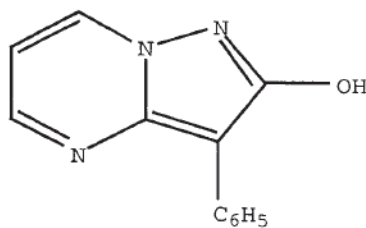
10 Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula



15 where R¹ is CF₃, C₂F₅, or C₆H₄F, and R² is CH₃, C₂H₅, CF₃, or C₆H₄F.

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

20



12

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

5

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

Other references which disclose azolopyrimidines
10 included 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
15 (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.

20

SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds which bind to corticotropin releasing factor receptors, thereby
25 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
30 disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic

13

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; dysthymia; 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)

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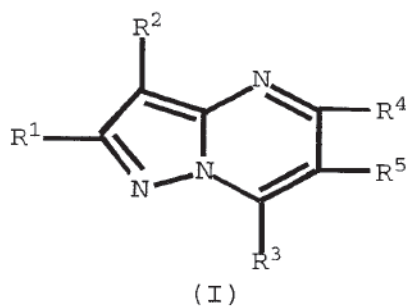
are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

5

DETAILED DESCRIPTION OF INVENTION

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

10



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

- R¹ is selected from the group consisting of
- C₁₋₆ alkyl,
 - 20 C₂₋₁₀ alkenyl,
 - C₂₋₁₀ alkynyl,
 - C₃₋₆ cycloalkyl,
 - C₁₋₆ alkyloxy,
 - C₁₋₆ alkylS(O)_n,
 - 25 -NR^{1a}R^{1b} wherein R^{1a} and R^{1b} are independently selected from
 - H, C₁₋₄ alkyl, -C(O)C₁₋₄alkyl,
 - C(O)NR^{1a}R^{1b},
 - O-C(O)C₁₋₄alkyl,

16

-XR^{1c} wherein R^{1c} is selected from H or -C₁₋₄ alkylaryl;
 X is selected from O or S(O)_n,

wherein R¹ is substituted with 0-6 substituents selected
 5 from halogen, C₁₋₄ alkyl, C₁₋₆ alkyloxy, C₁₋₄ haloalkyl, -
 NR^{1a}R^{1b}, -XR^{1c};

R² is selected from the group consisting of
 C₁₋₁₀ alkyl,
 10 C₂₋₁₀ alkenyl,
 C₂₋₁₀ alkynyl,
 C₃₋₈ cycloalkyl,
 C₃₋₆ cycloalkyl C₁₋₆ alkyl,
 C₁₋₁₀ alkyloxy,
 15 C₁₋₁₀ alkyloxyC₁₋₁₀ alkyl,
 C₁₋₄ alkoxy C₁₋₄ alkyl,
 -SO₂-C₁₋₁₀alkyl
 -SO₂R^{2a} wherein R^{2a} is aryl,
 -SO₂R^{2b} wherein R^{2b} is heteroaryl,
 20 -NR^{2c}R^{2d} wherein R^{2c} and R^{2d} are independently selected from
 H, C₁₋₈ alkyl, S(O)_nC₁₋₄ alkyl, C(O)NR^{2c}R^{2d}, CO₂C₁₋₄alkyl,
 C₃₋₈ cycloalkyl, C₁₋₆ alkyloxyC₁₋₆ alkyl, -C(O)C₁₋₄alkyl
 or R^{2c} and R^{2d} may join to form a heterocyclic ring
 having 0-3 heteroatoms selected from O, N or S,
 25
 - halogen,
 -CN,
 -C(O)L wherein L is selected from NR^{2c}R^{2d}, C₁₋₆ alkyl, H,
 -OC₁₋₆ alkyl, O(CH₂)_mOC₁₋₆alkyl, O(CH₂)_mNR^{2c}R^{2d}, -OH,
 30 aryl, heteroaryl or C(O)OC₁₋₆ alkyl, wherein m is 1-3,
 or more particularly from,
 -C(O)NR^{2c}R^{2d},
 -C(O)R wherein R is C₁₋₆ alkyl,

- C(O)OC₁₋₄ alkyl,
- C(O)O(CH₂)₂OR wherein R is C₁₋₃ alkyl,
- C(O)O(CH₂)₂-NHR wherein R is C₁₋₃ alkyl,
- C(O)O(CH₂)₂-NR²,
- 5 -C(O)OH,
- C(O)H,
- C(O)Ph,
- C(O)R' wherein R' is aryl, heteroaryl or carboalkoxy;

10

n is 0, 1 or 2;

- R² is substituted with 0-3 substituents independently selected from R', R'', R''' wherein R', R'' and R''' are
- 15 independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ alkyloxyC₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ alkyloxy, hydroxy, or

- R² is substituted with 0-3 substituents independently selected from:
- 20

halogen,

-CN,

-S(O)_nR^{2e} wherein R^{2e} is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl;

25

-COR^{2f} wherein R^{2f} is selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl, and C₃₋₆ cycloalkylC₁₋₄ alkyl;

30

-CO₂R^{2f},

-NR^{2g}COR^{2f} wherein R^{2g} is selected from H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ alkyloxy C₁₋₆ alkyl;

-N(COR^{2f})₂,

$-\text{NR}^{2g}\text{CONR}^{2f}\text{R}^{2h}$, 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;

5

$-\text{NR}^{2g}\text{CO}_2\text{R}^{2e}$,

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

1-morpholinyl,

1-piperidinyl,

10 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

$-\text{O}-$, $-\text{S}(\text{O})_n-$, $-\text{NR}^{2g}-$, $-\text{NCO}_2\text{R}^{2e}$, $-\text{NCOR}^{2e}$,

15 and $-\text{NSO}_2\text{R}^{2e}$; 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

20 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, $-\text{OR}^{2g}$,

$-\text{NR}^{2g}\text{R}^{2h}$, $-\text{C}_{1-6}$ alkyl OR^{2g} , and C_{3-8} cycloalkyl which is

substituted with 0-1 R^{2i} and in which 0-1 carbons of C_{4-8}

cycloalkyl is replaced by $-\text{O}-$, wherein

25 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, $-\text{CN}$,

30 nitro, $-\text{SH}$, $-\text{S}(\text{O})_n\text{R}^{2n}$, $-\text{COR}^{2m}$, $-\text{OC}(\text{O})\text{R}^{2n}$, $-\text{NR}^{2g}\text{COR}^{2m}$, -

$\text{N}(\text{COR}^{2m})_2$,

$-\text{NR}^{2g}\text{CONR}^{20}\text{R}^{2p}$, $-\text{NR}^{2g}\text{CO}_2\text{R}^{2n}$, $-\text{NR}^{2c}\text{R}^{2p}$ and $-\text{CONR}^{2e}\text{R}^{2p}$;

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} cycloalkyl- 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, $R^{2q}S(O)_n-C_{1-4}$ alkyl and $R^{2r}R^{2s}N-C_{2-4}$ alkyl;

5

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 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
10 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,
15 aryl(C_{1-4} alkyl), heteroaryl and heteroaryl (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;

20

$R^{2r}R^{2s}$ 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} ;

25

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);

30

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 C₁₋₆ alkyl, C₃₋₆ cycloalkyl, methylenedioxy, C₁₋₄ alkyloxy-C₁₋₄ alkyloxy, -OR^{2m}, Br, Cl, F, I, C₁₋₄ haloalkyl, -CN, -NO₂, -SH, -S(O)_nR²ⁿ, -COR^{2m}, -CO₂R^{2m}, -OC(O)R²ⁿ, -NR^{2g}COR^{2m}, -N(COR^{2m})₂, -NR^{2g}CONR^{2o}R^{2p}, -NR^{2g}CO₂R^{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 C₁₋₃ alkyl, C₁₋₃ alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF₃, C₂F₅, OCF₃, SO₂Me 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 substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C₁₋₆ alkyl, C₃₋₆ cycloalkyl, Br, F, I, C₁₋₄ haloalkyl, -CN, NR^{2g}R^{2h}, nitro, -OR^{2m}, -SH, -S(O)_nR²ⁿ, COR^{2m}, -CO₂R^{2m}, -OC(O)R²ⁿ, -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}, CO₂R^{3a}, COR^{3a} and SO₂R^{3a} wherein,

R^{3a} is selected from the group C₁₋₆ alkyl, C₁₋₄ cycloalkyl-C₁₋₆ alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group

C₁₋₄ alkyl, Br, Cl, F, I, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, and dimethylamino;

- R⁴ and R⁵ are independently selected at each occurrence
- 5 from H, Br, Cl, F, I, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₄ alkylamino, (C₁₋₄ alkyl)₂ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of C₁₋₇
- 10 alkyl, C₃₋₈ cycloalkyl, Br, Cl, F, I, -C(O)H, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₆ alkylamino and (C₁₋₄ alkyl)₂ amino and wherein R⁴ and R⁵ non-phenyl groups may be substituted with 0-5
- 15 substituents selected from OH, halogen, -C(O)H, -OC₁₋₆-alkyl and C₁₋₆ haloalkyl, C₁₋₆ alkyl, C₃₋₇ c-alkyl, C₁₋₆ alkyl(OH)_nCO₂R wherein R is H or C₁₋₆ alkyl, C₁₋₆ alkyl(OH)_n, wherein n is 0-3 or R⁴ and R⁵ may join together to form a C₃₋₆ alkylene chain; with the proviso that the compounds of
- 20 Formula I with R¹, R², R³, R⁴ and R⁵ as specifically defined below are excluded:

- (a) a compound of formula I wherein R¹ is unsubstituted, unbranched (linear) C₁₋₃ alkyl and R² is -C(O)-Ph (EP 0 129
- 25 847 A2, US 4,521,422, US 4,654,347);
- (b) a compound of formula I, wherein R⁵ is H or C₁₋₃ alkyl and R³ is pyridyl, pyridyl-N-oxide, thien-3-yl or furan-3-yl or C₁₋₃ alkyl substituted versions thereof and R¹ is carboamoyl or unsubstituted, unbranched C₁₋₃ alkyl, R² is
- 30 F, Cl, Br, formyl, carboxyl, CN, hydroxymethyl, unsubstituted, unbranched C₁₋₃ alkyl, -C(O)R, -C(O)OR, -CH₂OR, -C(O)O(CH₂)₂OR, -C(O)O(CH₂)₂NHR, or -C(O)O(CH₂)₂NR² wherein R is C₁₋₃ alkyl (US 4,281,000);

23

- (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)
- 5 (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
- 10 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,
- 15 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
- 20 (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
- 25 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
- 30 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);
- 10 (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);
- 15 (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_3Ph , R^4 and R^5 are H (reg. ref. 47);
- 20 (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);
- 25 (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);
- 30

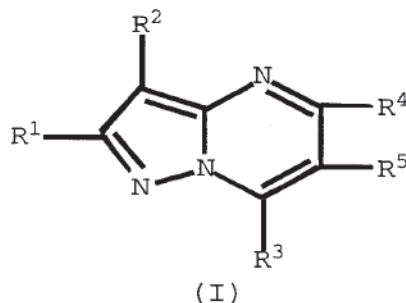
- (z) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OMe$ (reg. ref. 77);
- (aa) in a compound of formula I, R^2 is CH_3 , R^1 is CH_3 , R^3 is p-F-Ph, R^4 is c-propyl and R^5 is $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OH$ (reg. 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);
- 5 (ss) in a compound of formula I, R^2 is $C(O)OMe$, R^1 is -
SCH₂-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 -
SCH₂-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
10 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-CF₃-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);
- 15 (xx) in a compound of formula I, R^2 is CN, R^1 is SCH₃, 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 SCH₃, 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
20 pyrid-3-yl, R^4 and R^5 are H (reg. ref. 163);
- (aaa) in a compound of formula I, R^2 is CO₂H, 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 CO₂H, R^1 is CH₃, R^3
is pyrid-3-yl, R^4 and R^5 are H and H Cl salt (reg. ref.
25 165);
- (ccc) in a compound of formula I, R^2 is $C(O)OEt$, R^1 is CH₃,
 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 CH₃, R^3
is pyrid-3-yl, R^4 is H and R^5 is CH₃ (reg. ref. 167);
- 30 (eee) in a compound of formula I, R^2 is CN, R^1 is CH₃, 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);

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- (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);
- 5 (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
- 10 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);
- 15 (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)NH₂,
- 20 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
- 25 invention provides a novel compound of formula I:



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or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

- 5 R^1 is selected from the group consisting of
- C_{1-6} alkyl,
- C_{2-10} alkenyl,
- C_{2-10} alkynyl,
- 10 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,
- 15 $-C(O)NR^{1a}R^{1b}$,
- $-O-C(O)C_{1-4}$ alkyl,
- $-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;
- X is selected from O or S(O)_n,
- 20
- wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl, C_{1-6} alkyloxy, C_{1-4} haloalkyl, $-NR^{1a}R^{1b}$, $-XR^{1c}$;
- 25 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,
- 30 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,

- SO₂-C₁₋₁₀alkyl
 -SO₂R^{2a} wherein R^{2a} is aryl,
 -SO₂R^{2b} wherein R^{2b} is heteroaryl,
 -NR^{2c}R^{2d} wherein R^{2c} and R^{2d} are independently selected from
 5 H, C₁₋₈ alkyl, S(O)_nC₁₋₄ alkyl, C(O)NR^{2c}R^{2d}, CO₂C₁₋₄alkyl,
 C₃₋₈ cycloalkyl, C₁₋₆ alkyloxyC₁₋₆ alkyl, -C(O)C₁₋₄alkyl
 or R^{2c} and R^{2d} may join to form a heterocyclic ring
 having 0-3 heteroatoms selected from O, N or S,
- 10 n is 0, 1 or 2;
- R² is substituted with 0-3 substituents independently
 selected from R', R'', R''' wherein R', R'' and R''' are
 15 independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl,
 hydroxyC₁₋₆ alkyl, C₁₋₆ alkyloxyC₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆
 alkyloxy, hydroxy, or
- R² is substituted with 0-3 substituents independently
 20 selected from:
 -CN,
 -S(O)_nR^{2e} wherein R^{2e} is selected from C₁₋₄ alkyl, C₁₋₄
 haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl;
 25 -COR^{2f} wherein R^{2f} is selected from H, C₁₋₄ alkyl, C₁₋₄
 haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆
 cycloalkyl, and C₃₋₆ cycloalkylC₁₋₄ alkyl;
 -CO₂R^{2f},
 30 -NR^{2g}COR^{2f} wherein R^{2g} is selected from H, C₁₋₆ alkyl, C₃₋₇ c-
 alkyl, C₃₋₆ cycloalkyl C₁₋₆ alkyl;
 -N(COR^{2f})₂,
 -NR^{2g}CONR^{2f}R^{2h}, wherein R^{2h} is selected from H, C₁₋₆ alkyl,

30

C₁₋₄ haloalkyl, C₁₋₄ alkoxy C₁₋₄ alkyl,
C₃₋₆ cycloalkyl and C₃₋₆ cycloalkylC₁₋₆
alkyl;

- 5 -NR^{2g}CO₂R^{2e},
-CONR^{2g}R^{2h},
1-morpholinyl,
1-piperidinyl,
1-piperazinyl,
10 and
C₃₋₈ cycloalkyl wherein 0-1 carbon atoms in the C₄₋₈
cycloalkyl is replaced by a group selected from
-O-, -S(O)_n-, -NR^{2g}-, -NCO₂R^{2e}, -NCOR^{2e},
and -NSO₂R^{2e}; and wherein N₄ in
15 1-piperazinyl is substituted with 0-1
substituents selected from R^{2g}, CO₂R^{2e}, COR^{2e} and
SO₂R^{2e}; or

the group R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈
20 alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g},
-NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is
substituted with 0-1 R²¹ and in which 0-1 carbons of C₄₋₈
cycloalkyl is replaced by -O-, wherein

25 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,
30 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

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- 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, $-S(O)_nR^{2h}$, $-COR^{2m}$, -
- 5 $OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, -
 $NR^{2o}R^{2p}$ 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} ;
- 10 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, $-OR^{2m}$,
- 15 -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} ;
- 20
- wherein
- R^{21} is H, C_{1-4} alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl and C_{3-8} cycloalkyl;
- 25 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, $R^{2g}S(O)_n-C_{1-4}$ alkyl and $R^{2r}R^{2s}N-C_{2-4}$ alkyl;
- 30 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;

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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;

- 5 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 heteroaryl (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}
 10 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
 15 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,
 20 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;

- 25 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}
 30 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;

- 5 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-
 10 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 substituted at 0-4 carbon atoms with a substituent independently selected at
 15 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
 20 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
 25 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}
 30 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}

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alkyl, C₃₋₈ cycloalkyl, Br, Cl, F, I, -C(O)H, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₆ alkylamino and (C₁₋₄ alkyl)₂ amino and wherein R⁴ and R⁵ non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, -OC₁₋₆-alkyl and C₁₋₆ haloalkyl, C₁₋₆ alkyl, C₃₋₇ c-alkyl, C₁₋₆ alkyl(OH)_nCO₂R wherein R is H or C₁₋₆ alkyl, C₁₋₆ alkyl(OH)_n, wherein n is 0-3 or R⁴ and R⁵ may join together to form a C₃₋₆ alkylene chain.

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

R¹ is selected from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, -XR^{1c} wherein R¹ is substituted with 0-6 substituents selected from halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

R² is selected from substituted-C₁₋₁₀ alkyl, branched C₃₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₃₋₆ cycloalkyl C₁₋₆ alkyl, -NR^{2c}R^{2d} wherein, in the case of substituted-C₁₋₁₀ alkyl, 1-3 substituents are independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is substituted with 0-1 R²ⁱ and in which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O- and wherein the R² groups, other than substituted-C₁₋₁₀ alkyl, are substituted with 0-3 substituents independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is substituted with 0-1 R²ⁱ and in which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O-.

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[3] The present invention also relates to a compound described in groups [1], [1'] or [2] wherein R³ is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

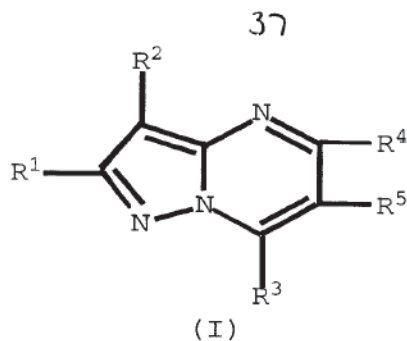
[4] The present invention relates to a compound described directly above in groups [1'] and [1]-[3] wherein R³ is substituted with 0-4 substituents independently selected from halogen, C₁₋₄ alkyloxy, C₁₋₆ alkyl or NR'R'' wherein R' and R'' are independently selected from H or C₁₋₆ alkyl.

[5] The present invention preferably relates to a compound as described directly above in groups [1'] and [1]-[4] wherein R³ 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 preferably relates to a compound as described in groups [1'] and [2]-[5] wherein R² is selected from C₁ alkyl of the formula -CR'R''R''' wherein R', R'' and R''' are independently selected from H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ alkyloxyC₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ alkyloxy, hydroxy, with the proviso that each of R', R'' and R''' cannot be H;

or R² is selected from NR^{2c}R^{2d} wherein R^{2c} and R^{2d} are independently selected from H or C₁₋₆ alkyl.

- [7] The present invention preferably 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 substituted 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 preferably relates to a compound of formula (I)



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

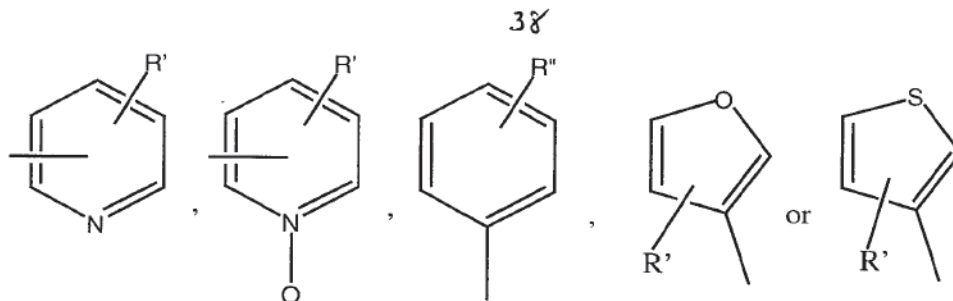
5 R^1 is selected from C_{1-6} alkyl, C_{1-6} alkyloxy, -SH or OH;

R^2 is selected from C_{1-4} alkyl which is unsubstituted or substituted with 1-4 substituents selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkylOR^{2g}, C_{2-6} alkenyl or OR^{2g}
 10 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,
 15 I, Br, -OH, CF₃, S(O)_nC₁₋₆ alkyl, -OC₁₋₆ 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
 20 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 C₁₋₃ alkyl and R'' is H or o-
 5 trifluoromethyl, m-trifluoromethyl or m-methoxy (see
 4,281,000).

[9] The present invention also relates to a compound
 according to group [8] wherein R³ is substituted with 2-4
 10 substituents.

[10] The present invention also relates to a compound
 according to group [8] or [9] wherein R² is substituted
 with 1-4 substituents.

15

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

20 [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-
 25 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} 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 O 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,

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- C_{2-10} alkenyl,
 C_{2-10} alkynyl,
 C_{3-8} cycloalkyl,
 C_{3-6} cycloalkyl C_{1-6} alkyl,
5 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,
10 $-SO_2R^{2b}$ 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
15 from O, N or S,

- halogen,
-CN,
 $-C(O)NR^{2c}R^{2d}$,
20 $-C(O)R$ 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,
 $-C(O)O(CH_2)_2-NR^2$,
25 $-C(O)OH$,
 $-C(O)H$,
 $-C(O)Ph$,
 $-C(O)R'$ wherein R' is aryl, heteroaryl or carboalkoxy;
30
n is 0, 1 or 2;

R^2 is substituted with 0-3 substituents independently

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- 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
- 5 R^2 is substituted with 0-3 substituents independently selected from
- halogen,
- CN,
- 10 $-S(O)_n R^{2e}$ 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;
- 15 $-CO_2 R^{2f}$,
- $-NR^{2g} COR^{2f}$ wherein R^{2g} is selected from H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl;
- $-N(COR^{2f})_2$,
- 20 $-NR^{2g} CONR^{2f} R^{2h}$, 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;
- $-NR^{2g} CO_2 R^{2e}$,
- 25 $-CONR^{2g} R^{2h}$,
- 1-morpholinyl,
- 1-piperidinyl,
- 1-piperazinyl,
- and
- 30 C_{3-8} cycloalkyl wherein 0-1 carbon atoms in the C_{4-8} cycloalkyl is replaced by a group selected from
- $-O-$, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2 R^{2e}$, $-NCOR^{2e}$, and $-NSO_2 R^{2e}$; and wherein N_4 in

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- 1-piperazinyl is substituted with 0-1 substituents selected from R^{2g} , CO_2R^{2e} , COR^{2e} and SO_2R^{2e} ; or
- 5 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^{2i} and in which 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O-, wherein
- 10 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, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, -
- 15 $N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2n}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$;
- R^{2j} is selected from heteroaryl wherein heteroaryl
- 20 includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-
- 25 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
- 30 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
 5 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, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$,
 10 $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ 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} ;

15 wherein

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

20 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, $R^{2g}S(O)_n-C_{1-4}$ alkyl and $R^{2x}R^{2s}N-C_{2-4}$ alkyl;

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl-
 25 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;

30

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 heteroaryl (C_{1-4} alkyl)-

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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;

5

$R^{2r}R^{2s}$ 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} ,

10

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);

15

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, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2q}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2q}CONR^{2o}R^{2p}$, $-NR^{2q}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ 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;

30

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

- 45
- 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, indolyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted 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, -
- 10 $S(O)_nR^{2n}$, 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,
- 15 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;
- 20 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, 25 $(C_{1-4} \text{ alkyl})_2$ 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} 30 alkylamino and $(C_{1-4} \text{ alkyl})_2$ 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}

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alkyl(OH)_nCO₂R wherein R is H or C₁₋₆ alkyl, C₁₋₆ alkyl(OH)_n, wherein n is 0-3 or R⁴ and R⁵ may join together to form a C₃₋₆ alkylene chain.

5 [13] The present invention also relates to a method as described directly above in group [12] wherein

R¹ is selected from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, -XR^{1c} wherein R¹ is substituted with 0-6 substituents selected from halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

R² is selected from substituted-C₁₋₁₀ alkyl, branched C₃₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₃₋₆ cycloalkyl C₁₋₆ alkyl, -NR^{2c}R^{2d} wherein, in the case of substituted-C₁₋₁₀ alkyl, 1-3 substituents are

15 independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is substituted with 0-1 R²ⁱ and in which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O- and wherein the R²

20 groups, other than substituted-C₁₋₁₀ alkyl, are substituted with 0-3 substituents independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is substituted with 0-1 R²ⁱ and in

25 which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O-.

[14] The present invention also relates to a method described directly above in [12] or [13] wherein R³ is selected from an aryl group selected from phenyl or

30 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 preferably 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.

15

[17] The present invention also preferably 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 preferably 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}

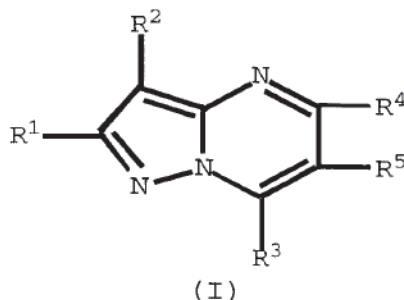
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alkyloxy-C₁₋₄, alkyloxy, -OR^{2m}, Br, Cl, F, I, C₁₋₄ haloalkyl, -CN, -NO₂, -SH, -S(O)_nR²ⁿ, -COR^{2m}, -CO₂R^{2m}, -OC(O)R²ⁿ, -NR^{2g}COR^{2m}, -N(COR^{2m})₂, -NR^{2g}CONR^{2o}R^{2p}, -NR^{2g}CO₂R^{2h}, -NR^{2o}R^{2p} and CONR^{2o}R^{2p} and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group C₁₋₃ alkyl, C₁₋₃ alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF₃, C₂F₅, OCF₃, SO₂Me and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C₁₋₆ alkyl, C₃₋₆ cycloalkyl, Br, F, I, C₁₋₄ haloalkyl, -CN, nitro, -OR^{2m}, -SH, -S(O)_nR²ⁿ, COR^{2m}, -CO₂R^{2m}, -OC(O)R²ⁿ, -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}, CO₂R^{3a}, COR^{3a} and SO₂R^{3a}.

[19] The present invention preferably 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

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



5

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;
10

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

15

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, CF₃, S(O)_nC₁₋₆ alkyl, -OC₁₋₆ 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;
20

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.

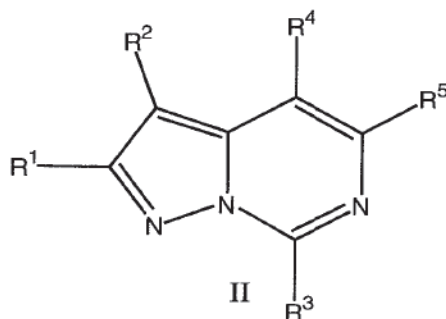
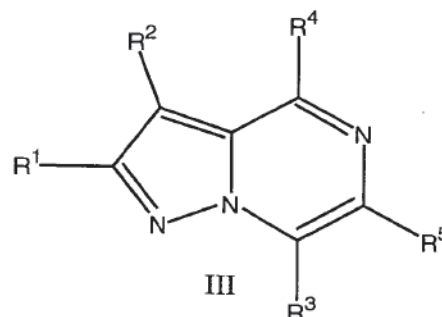
5 [21] The present invention also relates to a method according to group [19]-[20] wherein R^2 is substituted with 1-4 substituents.

[22] The present invention also relates to a method
10 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
15 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.

20 [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
25 of the formulae shown below having the variables recited above in groups [1'] and [1]-[24]:



except that the provisos listed in group I are not
30 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

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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
5 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,
10 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
15 that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are
20 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
25 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
30 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
35 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

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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:

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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-

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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-ethylpyrazolo[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-methylpyrazolo[1,5-a]pyrimidine

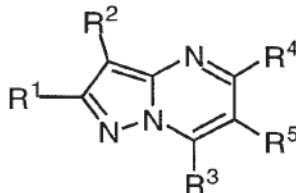
2-ethyl-3-(3-heptyl)-7-(2,4,6-trimethylphenyl)-
 pyrazolo[1,5-a]pyrimidine
 7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-pyrazolo[1,5-
 a]pyrimidine
 7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-6-methyl-
 pyrazolo[1,5-a]pyrimidine
 2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethylphenyl)-
 pyrazolo[1,5-a]pyrimidine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

Synthesis

5 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.

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

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



may be prepared according to the following methods:

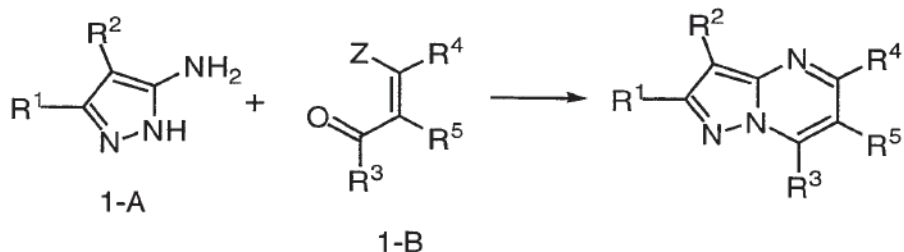
The pyrazolo[1,5-a]pyrimidine ring system is best
 prepared by the condensation reaction of a 3-
 20 aminopyrazole (1-A, Scheme 1A) with a compound of formula

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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

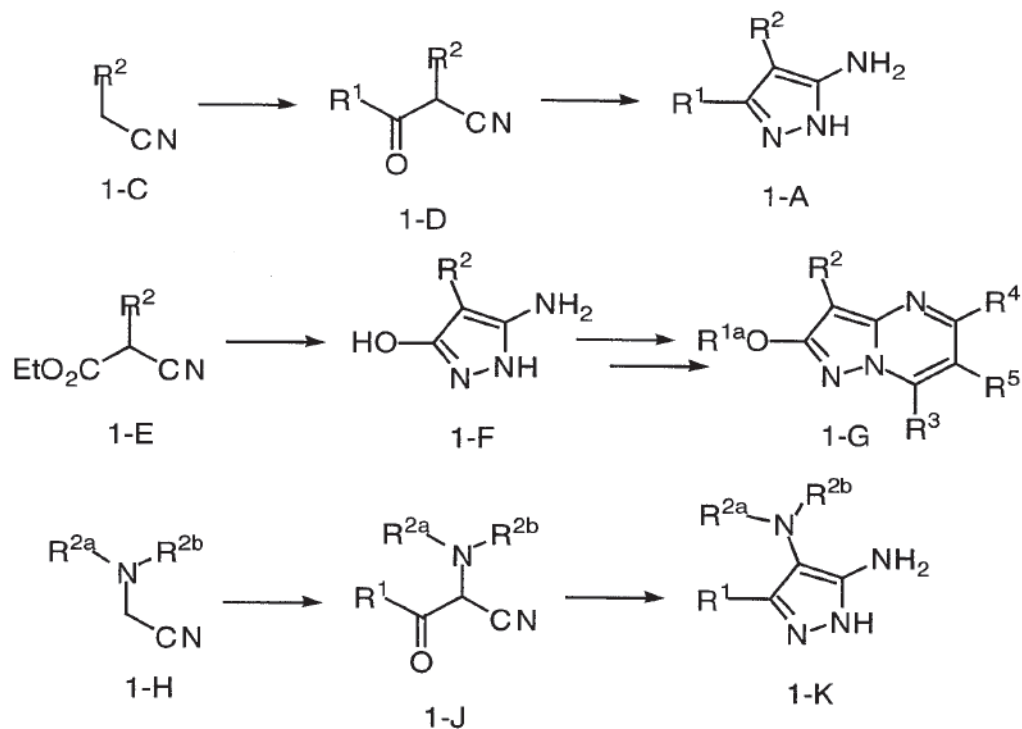


acid chloride R^1COCl to generate the ketonitrile 1-D. Condensation of this compound with hydrazine then gives the aminopyrazole. This reaction may be performed in refluxing alcoholic solvent with the optional presence of an acid catalyst, such as acetic acid. Heteroatomic versions of this route are 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.

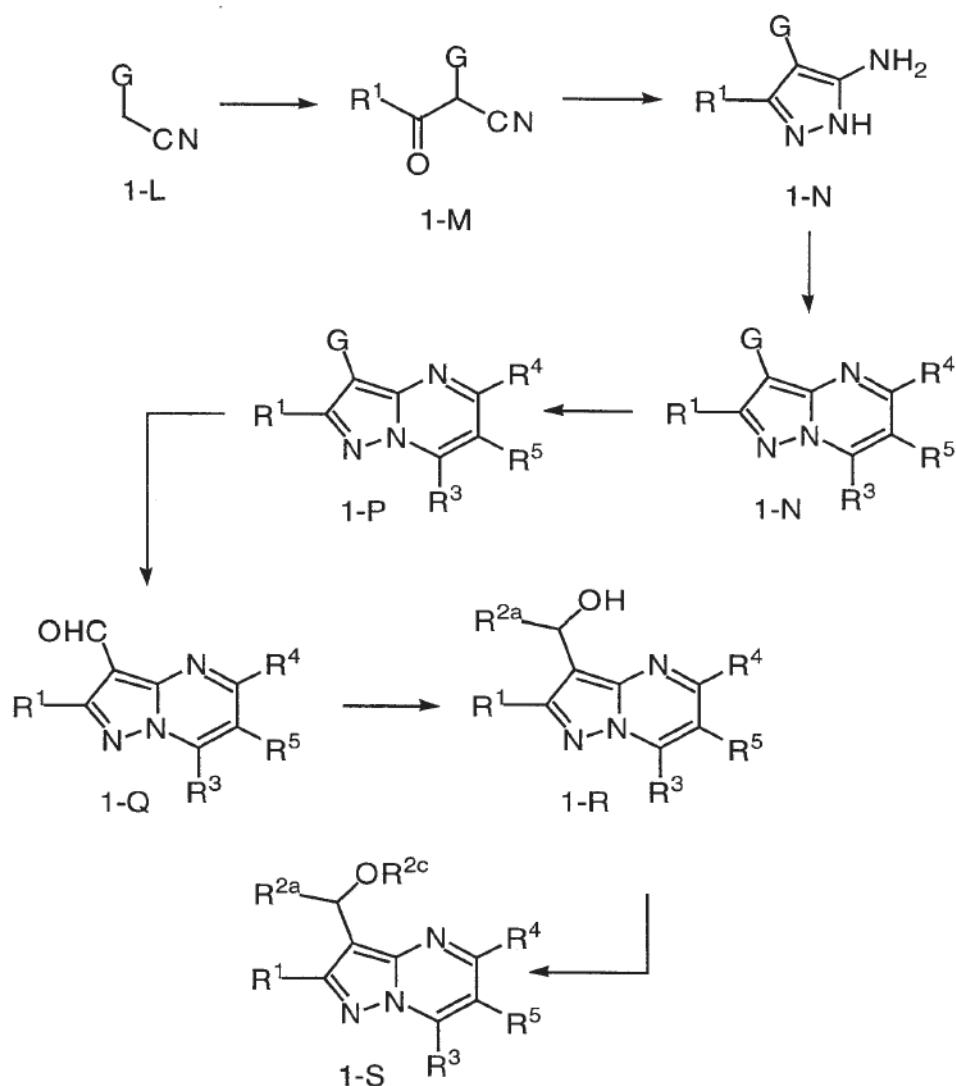
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Cyclization with reagent 1-B and O-alkylation with a reagent $R^{1a}X$, wherein X is a halide or pseudohalide group, gives compound 1-G. Finally, strong base treatment of aminonitrile 1-H, usually in the presence of a solvent mixture such as THF/HMPA,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

Scheme 1B



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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 R² 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 R² group of

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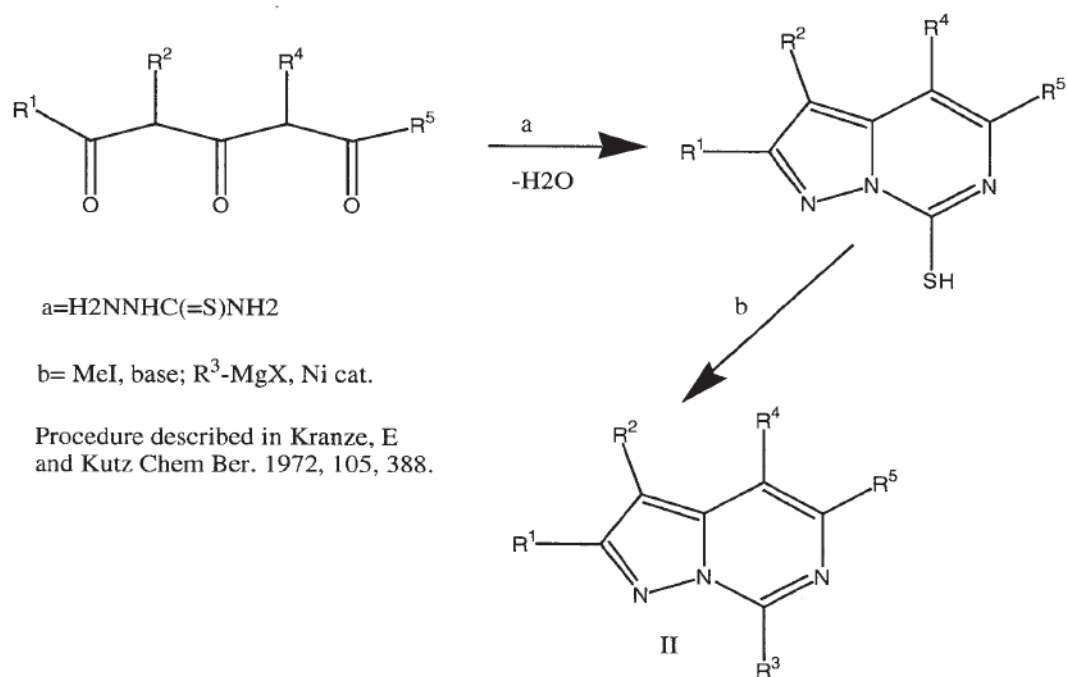
choice wherein R^2 and substituted versions thereof is as defined in the claims and as above in the specification; the following method is one example. Use of a reducing agent such as diisobutylaluminum hydride in a solvent like toluene or dichloromethane at low temperatures can be used to obtain the 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.

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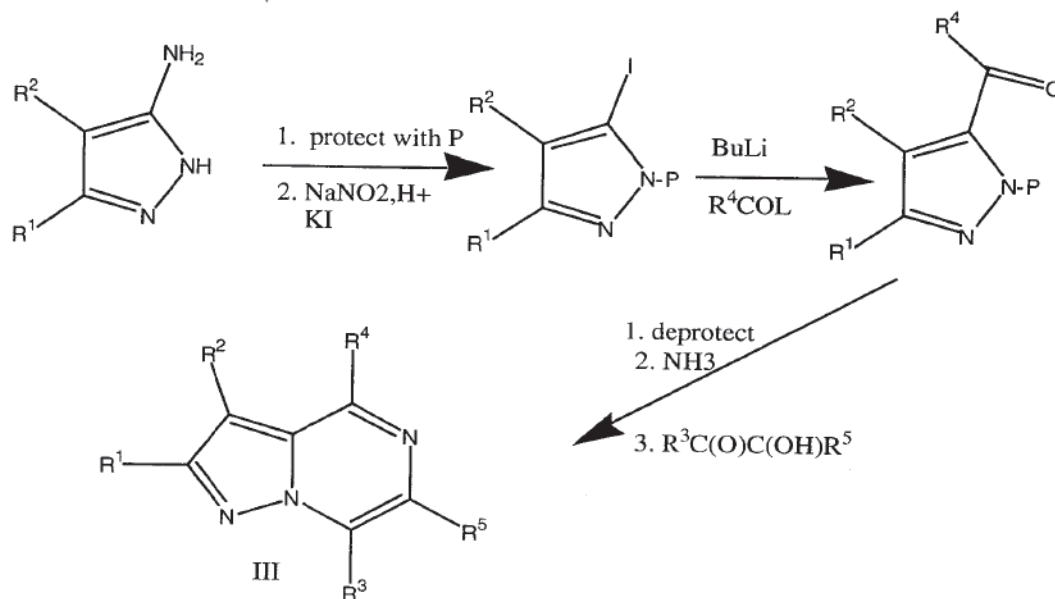
SCHEME 2



The variables for $\text{R}^1\text{-R}^5$ 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
 5 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.

10

Utility

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

15

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 CRH₁ receptor using a modified version of methods described earlier (see E.B. DeSouza, J. Neurosci, 7:88, 1987). Rat cortex was homogenized in
5 tissue buffer (containing 50 mM HEPES, 10 mM MgCl₂, 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
10 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
15 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
20 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, [¹²⁵I] tyr^o ovine CRH; New England
25 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
30 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,
35 containing 0.01% Triton X-100), dried, and counted in a gamma counter at 80% efficiency.

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Binding affinities (K_i 's) of ligands for the CRH₁ 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 MgCl₂, 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/³²P]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 [³H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [³²P]cAMP from [³²P]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

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

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

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

10 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
15 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
20 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
25 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
30 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.

35 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

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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
5 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
10 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
15 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
20 disintegration of the tablet in the gastrointestinal tract.

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

25 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
30 administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are
35 suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as

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

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

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

10

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.

15

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
20 displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

25 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
30 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.

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

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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: ¹H NMR (300 MHz, CDCl₃): δ 2.33 (2H, d, J = 5.8 Hz), 1.62-1.36 (5H, m), 0.92 (6H, t, J = 7.3 Hz). MS (H₂O-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: ^1H 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: ^1H 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

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product, which was the title compound. TLC R_f 0.32 (10:90 ethyl acetate-hexane). Spectral data: ¹H NMR (300 MHz, CDCl₃): 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 (NH₃-CI): m/e 367 (2), 366 (11), 365 (15), 364 (65), 363 (25), 362 (100). Analysis calc'd for C₁₉H₂₁Cl₂N₃: 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 31Preparation of 7-(2,4-dichlorophenyl)-3-(N,N-diethylamino)-2-ethylpyrazolo[1,5-a]pyrimidine

- 5 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
- 10 -78 °C. To this was added first, N,N'-dimethylpropyleneurea as cosolvent (15 mL), then, diethylaminoacetonitrile (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
- 15 the resulting mixture was allowed to stir and warm to ambient temperature for 12 hours. It was poured into 200 mL of satd. aq. NH₄Cl solution, and this was extracted with ethyl acetate (2 x 200 mL). The extracts were combined, dried over magnesium sulfate, filtered and
- 20 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%).
- 25 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)
- 30 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. NaHCO₃ 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%).
- 10 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 column chromatography (silica gel, 20:80 ethyl acetate-hexane) to afford the title product as a red oil (411 mg, 1.13 mmol, 64%).
- 20 Spectral data: ¹H NMR (300 MHz, CDCl₃): 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 (NH₃-CI): calculated for C₁₈H₂₁Cl₂N₄ 363.1143, measured 363.1146; m/e 367 (6), 366 (14), 365 (81), 364 (28), 363 (100).
- 30 Examples 32-45 were and/or may be prepared in an analogous manner.

Examples 51 and 92

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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)

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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: ^1H 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 NaHCO₃, 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: ¹H NMR (300 MHz, CDCl₃): 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: ¹H NMR (300 MHz, CDCl₃): 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 (NH₃-CI): m/e

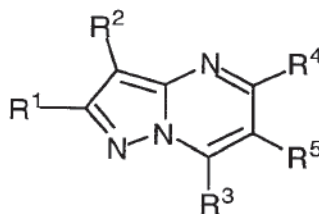
383 (2), 382 (12), 381 (14), 380 (65), 379 (25), 378 (100).

Examples 52-90 and 92 were and/or may be prepared according to the procedures described above. The
5 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.

10

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Table 1



<u>Ex</u> <u>No</u>	<u>R¹</u>	<u>R²</u>	<u>R⁴</u>	<u>R⁵</u>	<u>R³</u>	<u>m.p.</u> <u>°C</u>
1	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2,4-Cl ₂ -C ₆ H ₃	oil ^a
2	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	88- 89
3	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	oil ^b
4	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	166- 167
5	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
6	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	90- 91
7	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
8	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
9	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
10	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
11	C ₂ H ₅	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
12	C ₂ H ₅	(C ₂ H ₅) ₂ CH	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
13	C ₂ H ₅	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
14	C ₂ H ₅	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
15	C ₂ H ₅	(C ₂ H ₅) ₂ CH	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
16	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4-Cl ₂ -C ₆ H ₃	oil ^c
17	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
18	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	oil ^d
19	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-

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20	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
21	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	78- 79
22	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
23	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
24	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
25	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
26	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
27	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
28	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
29	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
30	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
31	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2,4-Cl ₂ -C ₆ H ₃	oil ^o
32	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	97- 98
33	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
34	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
35	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
36	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	-
37	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
38	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
39	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
40	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
41	C ₂ H ₅	(C ₂ H ₅) ₂ N	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
42	C ₂ H ₅	(C ₂ H ₅) ₂ N	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
43	C ₂ H ₅	(C ₂ H ₅) ₂ N	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
44	C ₂ H ₅	(C ₂ H ₅) ₂ N	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-

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45	C ₂ H ₅	(C ₂ H ₅) ₂ N	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
46	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
47	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
48	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
49	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
50	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
51	OCH ₃	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	oil ^f
52	OCH ₃	(C ₂ H ₅) ₂ CH	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
53	OCH ₃	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
54	OCH ₃	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
55	OCH ₃	(C ₂ H ₅) ₂ CH	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
56	OCH ₃	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
57	OCH ₃	(C ₂ H ₅) ₂ CH	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
58	OCH ₃	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
59	OCH ₃	(C ₂ H ₅) ₂ CH	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
60	OCH ₃	(C ₂ H ₅) ₂ CH	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
61	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
62	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
63	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
64	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
65	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
66	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	-
67	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
68	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
69	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
70	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ -	-

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					pyridin-5-yl	
71	OCH ₃	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
72	OCH ₃	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
73	OCH ₃	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
74	OCH ₃	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
75	OCH ₃	C ₄ H ₉ (C ₂ H ₅) CH	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
76	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2,4-Cl ₂ -C ₆ H ₃	-
77	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
78	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
79	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
80	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
81	OCH ₃	(C ₂ H ₅) ₂ N	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	-
82	OCH ₃	(C ₂ H ₅) ₂ N	H	CH ₃	2-Cl-4-CH ₃ O-C ₆ H ₃	-
83	OCH ₃	(C ₂ H ₅) ₂ N	H	CH ₃	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
84	OCH ₃	(C ₂ H ₅) ₂ N	H	CH ₃	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
85	OCH ₃	(C ₂ H ₅) ₂ N	H	CH ₃	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
86	OCH ₃	(C ₂ H ₅) ₂ N	CH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
87	OCH ₃	(C ₂ H ₅) ₂ N	CH ₃	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
88	OCH ₃	(C ₂ H ₅) ₂ N	CH ₃	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
89	OCH ₃	(C ₂ H ₅) ₂ N	CH ₃	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
90	OCH ₃	(C ₂ H ₅) ₂ N	CH ₃	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
91	CH ₃	(C ₂ H ₅) ₂ CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
92	OH	(C ₂ H ₅) ₂ CH	H	CH ₃	2,4-Cl ₂ -C ₆ H ₃	227- 228
93	C ₂ H ₅	(C ₂ H ₅) ₂ CH	OCH ₃	H	2,4-Cl ₂ -C ₆ H ₃	-
94	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	OCH ₃	2,4-Cl ₂ -C ₆ H ₃	-
95	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
96	C ₂ H ₅	CH ₃ (c-C ₃ H ₅) CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-

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97	C ₂ H ₅	CH ₃ (c-C ₄ H ₇) CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
98	C ₂ H ₅	(c-C ₃ H ₅) ₂ CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
99	C ₂ H ₅	C ₂ H ₅ (c-C ₃ H ₅) CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
100	C ₂ H ₅	CH ₃ (c-C ₄ H ₇) CH	H	H	2,4-Cl ₂ -C ₆ H ₃	-
101	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2,4-Cl ₂ -C ₆ H ₃	-
102	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
103	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
104	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
105	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
106	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
107	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4-OCH ₃ -5-F	-
108	C ₂ H ₅	(HOCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4,5-(OCH ₃) ₂	-
109	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2,4-Cl ₂ -C ₆ H ₃	-
110	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
111	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
112	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
113	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
114	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
115	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4-OCH ₃ -5-F	-
116	C ₂ H ₅	(CH ₃ OCH ₂) ₂ (CH ₃) C	H	H	2-Cl-4,5-(OCH ₃) ₂	-
117	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃) C	H	H	2,4-Cl ₂ -C ₆ H ₃	-

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118	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
119	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
120	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
121	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
122	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
123	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2-Cl-4-OCH ₃ -5-F	-
124	C ₂ H ₅	(H ₂ C=CH) ₂ (CH ₃)C	H	H	2-Cl-4,5-(OCH ₃) ₂	-
125	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2,4-Cl ₂ -C ₆ H ₃	-
126	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
127	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
128	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
129	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
130	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
131	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2-Cl-4-OCH ₃ -5-F	-
132	C ₂ H ₅	(c-C ₃ H ₅) ₂ (CH ₃)C	H	H	2-Cl-4,5-(OCH ₃) ₂	-
133	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2,4-Cl ₂ -C ₆ H ₃	-
134	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
135	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
136	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
137	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
138	C ₂ H ₅	(C ₂ H ₅) ₂ (OH)C	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-

139	C ₂ H ₅	(C ₂ H ₅) ₂ (OH) C	H	H	2-Cl-4-OCH ₃ -5-F	-
140	C ₂ H ₅	(C ₂ H ₅) ₂ (OH) C	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
141	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2, 4-Cl ₂ -C ₆ H ₃	-
142	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
143	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2, 4, 6- (CH ₃) ₃ -C ₆ H ₂	-
144	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2, 4, 6- (OCH ₃) ₃ - C ₆ H ₂	-
145	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2- (CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
146	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	-
147	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2-Cl-4-OCH ₃ -5-F	-
148	C ₂ H ₅	C ₂ H ₅ (OCH ₃) CH	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
149	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	oil
150	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-OCH ₃ -5-F	-
151	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
152	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	-
153	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	H	2-Cl-4-OCH ₃ -5-F	-
154	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅) CH	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
155	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	oil ^g
156	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-OCH ₃ -5-F	-
157	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
158	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	-
159	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-Cl-4-OCH ₃ -5-F	-
160	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
161	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
162	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2, 4, 6- (CH ₃) ₃ -C ₆ H ₂	-
163	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2, 4, 6- (OCH ₃) ₃ - C ₆ H ₂	-
164	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2- (CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
165	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2, 4-Cl ₂ -5-F-C ₆ H ₂	-
166	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2-Cl-4-OCH ₃ -5-F	-
167	C ₂ H ₅	C ₃ H ₇ (CH ₃) CH	H	H	2-Cl-4, 5- (OCH ₃) ₂	-
168	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-CH ₃ -4-OCH ₃ -5-	-

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169	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -5-	-
170	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -5-	-
171	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -5-	-
172	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -5-	-
173	OCH ₃	(C ₂ H ₅) ₂ N	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -5-	-
174	C ₂ H ₅	C ₃ H ₇ (CH ₃)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -5-	-
175	OCH ₃	C ₃ H ₇ (CH ₃)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -5-	-
176	C ₂ H ₅	C ₂ H ₅ (OCH ₃)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -5-	-
177	OCH ₃	C ₂ H ₅ (OCH ₃)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -5-	-
178	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
179	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
180	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
181	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
182	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
183	OCH ₃	(C ₂ H ₅) ₂ N	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
184	C ₂ H ₅	C ₃ H ₇ (CH ₃)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
185	OCH ₃	C ₃ H ₇ (CH ₃)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
186	C ₂ H ₅	C ₂ H ₅ (OCH ₃)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
187	OCH ₃	C ₂ H ₅ (OCH ₃)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
188	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-Cl-C ₆ H ₃	-
189	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-Cl-C ₆ H ₃	-
190	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-Cl-C ₆ H ₃	-
191	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	F-C ₆ H ₂ 2-CH ₃ -4-Cl-C ₆ H ₃	-

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192	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
193	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
194	C ₂ H ₅	C ₃ H ₇ (CH ₃)CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
195	OCH ₃	C ₃ H ₇ (CH ₃)CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
196	C ₂ H ₅	C ₂ H ₅ (OCH ₃)CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
197	OCH ₃	C ₂ H ₅ (OCH ₃)CH	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
198	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	oil ^h
199	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
200	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
201	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
202	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
203	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
204	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
205	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
206	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
207	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -5- F-C ₆ H ₂	-
208	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
209	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
210	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	-
211	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
212	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
213	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
214	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
215	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-

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216	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
217	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
218	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
219	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -5-F-C ₆ H ₂	-
220	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
221	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
222	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	-
223	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
224	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
225	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ -C ₆ H ₂	-
226	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-(CH ₃) ₂ N-4-CH ₃ -pyridin-5-yl	-
227	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ -C ₆ H ₂	-
228	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
229	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
230	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
231	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -5-F-C ₆ H ₂	-
232	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
233	C ₂ H ₅	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
234	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	-
235	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
236	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
237	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ -C ₆ H ₂	-
238	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C	H	H	2-(CH ₃) ₂ N-4-CH ₃ -	-

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		H			pyridin-5-yl	
239	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
240	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
241	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
242	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
243	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -5- F-C ₆ H ₂	-
244	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
245	OCH ₃	C ₂ H ₅ OCH ₂ (CH ₃)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
246	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	-
247	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
248	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-
249	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
250	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
251	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
252	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
253	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
254	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
255	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-OCH ₃ -5- F-C ₆ H ₂	-
256	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
257	C ₂ H ₅	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
258	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4-Cl ₂ -C ₆ H ₃	-
259	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4-CH ₃ O-C ₆ H ₃	-
260	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(CH ₃) ₃ -C ₆ H ₂	-

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261	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
262	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-(CH ₃) ₂ N-4-CH ₃ - pyridin-5-yl	-
263	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4,6-(OCH ₃) ₃ - C ₆ H ₂	-
264	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2,4-Cl ₂ -5-F-C ₆ H ₂	-
265	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4-OCH ₃ -5-F	-
266	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-Cl-4,5-(OCH ₃) ₂	-
267	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-OCH ₃ -5- F-C ₆ H ₂	-
268	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-OCH ₃ -C ₆ H ₃	-
269	OCH ₃	CH ₃ OCH ₂ (C ₂ H ₅)C H	H	H	2-CH ₃ -4-Cl-C ₆ H ₃	-
270	C ₂ H ₅	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	oil ⁱ
271	OCH ₃	(C ₂ H ₅) ₂ CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
272	C ₂ H ₅	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
273	OCH ₃	C ₄ H ₉ (C ₂ H ₅)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
274	C ₂ H ₅	(C ₂ H ₅) ₂ N	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
275	OCH ₃	(C ₂ H ₅) ₂ N	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
276	C ₂ H ₅	C ₃ H ₇ (CH ₃)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
277	OCH ₃	C ₃ H ₇ (CH ₃)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
278	C ₂ H ₅	C ₂ H ₅ (OCH ₃)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
279	OCH ₃	C ₂ H ₅ (OCH ₃)CH	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
280	C ₂ H ₅	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-
281	OCH ₃	CH ₃ OCH ₂ (CH ₃)C H	H	H	2-Cl-4-CF ₃ -C ₆ H ₃	-

Key:

- a) Spectral data for Example 1: ¹H NMR (300 MHz, CDCl₃): δ
- 5 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

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- (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 ($\text{NH}_3\text{-CI}$): m/e 367 (2), 366 (11), 365 (15), 364 (65), 363 (25), 362 (100). Analysis calc'd for $\text{C}_{19}\text{H}_{21}\text{Cl}_2\text{N}_3$: 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: ^1H 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 ($\text{NH}_3\text{-CI}$): m/e 338 (3), 337 (24), 336 (100). Analysis calc'd for $\text{C}_{22}\text{H}_{29}\text{N}_3$: 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: ^1H 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 ($\text{NH}_3\text{-CI}$): m/e calculated for $\text{C}_{21}\text{H}_{26}\text{Cl}_2\text{N}_3$: 390.1504, found 390.1502; 395 (3), 394 (12), 393 (17), 392 (67), 391 (29), 390 (100).
- d) Spectral data for Example 18: ^1H 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 ($\text{NH}_3\text{-CI}$): m/e calc'd for $\text{C}_{24}\text{H}_{34}\text{N}_3$: 364.2753, found 364.2754; 366 (4), 365 (27), 364 (100).
- e) Spectral data for Example 31: ^1H 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

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(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 ($\text{NH}_3\text{-CI}$): calculated for $\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{N}_4$: 363.1143, found 363.1146; m/e 367 (6), 366 (14), 365 (81), 364

5 (28), 363 (100).

f) Spectral data for Example 51: ^1H 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

10 (6H, t, $J = 7.4$ Hz). MS ($\text{NH}_3\text{-CI}$): m/e 383 (2), 382 (12), 381 (14), 380 (65), 379 (25), 378 (100).

g) Spectral data for Example 155: ^1H 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

15 (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 ($\text{NH}_3\text{-CI}$): m/e 384 (11), 383 (16), 382 (79), 381 (20), 380 (100).

h) Spectral data for Example 198: ^1H 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

20 Spectrum (AP-CI): m/e 364 (100), 366 (65), 368 (12.5). High resolution mass spectrum: for $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{N}_3\text{O}$ m/e calculated: 364.0984, observed 364.0988.

i) Spectral data for Example 270: TLC R_f 0.19 (5:95 ethyl acetate-hexane). ^1H 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).

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MS (NH₃-CI): m/e 399 (7), 398 (33), 397 (25), 396 (100).
Analysis calc'd for C₂₀H₂₁ClF₃N₃: 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-

alpyrimidine

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

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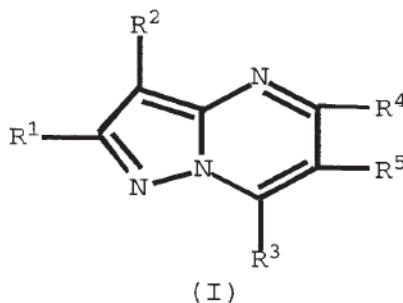
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-3-butyl)pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-methoxy-3-butyl)pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-pyrazolo[1,5-a]pyrimidine
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-6-methyl-pyrazolo[1,5-a]pyrimidine
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
5 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
10 variation without departing from the spirit of the
invention, the full scope of which is delineated by the
appended claims.

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WHAT IS CLAIMED IS:

1. A compound of formula I:



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or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of

10 C_{1-6} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkyloxy,15 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,

20 $-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;

X is selected from O 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, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

25

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,
5 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
10 H, C_{1-8} alkyl, $S(O)_n C_{1-4}$ 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,

15 - halogen,
-CN,
 $-C(O)L$ wherein L is selected from $NR^{2c}R^{2d}$, C_{1-6} alkyl, H,
 $-OC_{1-6}$ alkyl, $O(CH_2)_m OC_{1-6}$ alkyl, $O(CH_2)_m NR^{2c}R^{2d}$, -OH, aryl,
heteroaryl or $C(O)OC_{1-6}$ alkyl wherein m is 1-3;
20

n is 0, 1 or 2;

 R^2 is substituted with 0-3 substituents independently
25 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

30 R^2 is substituted with 0-3 substituents independently
selected from
halogen,
-CN,

- C_{1-6}
- S(O)_nR^{2e} wherein R^{2e} is selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl;
- 5 -COR^{2f} wherein R^{2f} is selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkyloxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl, and C₃₋₆ cycloalkylC₁₋₄ alkyl;
- CO₂R^{2f},
- NR^{2g}COR^{2f} wherein R^{2g} is selected from H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ cycloalkyl C₁₋₆ alkyl;
- 10 -N(COR^{2f})₂,
- NR^{2g}CONR^{2f}R^{2h}, wherein R^{2h} is selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy C₁₋₄ alkyl, C₃₋₆ cycloalkyl and C₃₋₆ cycloalkylC₁₋₆ alkyl;
- 15 -NR^{2g}CO₂R^{2e},
- CONR^{2g}R^{2h},
- 1-morpholinyl,
- 1-piperidinyl,
- 20 1-piperazinyl,
- and
- C₃₋₈ cycloalkyl wherein 0-1 carbon atoms in the C₄₋₈ cycloalkyl is replaced by a group selected from
- O-, -S(O)_n-, -NR^{2g}-, -NCO₂R^{2e}-, -NCOR^{2e}-,
- 25 and -NSO₂R^{2e}; and wherein N₄ in
- 1-piperazinyl is substituted with 0-1 substituents selected from R^{2g}, CO₂R^{2e}, COR^{2e} and SO₂R^{2e}; or
- 30 the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is substituted with 0-1 R²ⁱ and in which 0-1 carbons of C₄₋₈

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- 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
- 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 $-CONR^{2o}R^{2p}$;
- 10 R^{2j} is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl,
- 15 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
- 20 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
- 25 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
- 30 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, $-OR^{2m}$,

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-SH, $-S(O)_n R^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$,
 $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ 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}
5 and SO_2R^{2e} ;

wherein

R^{2i} is H, C_{1-4} alkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl and C_{3-8}
10 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, $R^{2q}S(O)_n-C_{1-4}$ alkyl
and $R^{2r}R^{2s}N-C_{2-4}$ alkyl;

15

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 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
20 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,
25 aryl(C_{1-4} alkyl), heteroaryl and heteroaryl (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;

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$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-
morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N_4 in

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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
 5 $-C_{1-4}$ 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
 10 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
 15 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
 20 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,
 25 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 substituted at 0-4
 30 carbon atoms with a substituent independently selected at

for

- 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
- 5 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
- 10 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
- 15 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, $(C_{1-4} \text{ alkyl})_2$ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of C_{1-7}
- 20 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 $(C_{1-4} \text{ alkyl})_2$ amino and wherein R^4 and R^5 non-phenyl groups may be substituted with 0-5
- 25 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) $_n$ CO $_2$ R 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
- 30 Formula I with R^1 , R^2 , R^3 , R^4 and R^5 as specifically defined below are excluded:

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- (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, $-C(O)R$, $-C(O)OR$, $-CH_2OR$, $-C(O)O(CH_2)_2OR$, $-C(O)O(CH_2)_2NHR$, or $-C(O)O(CH_2)_2NR^2$ wherein R is C_{1-3} alkyl;
- (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_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;
- (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_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;
- (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;

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- (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 ;
- 5 (k) in a compound of formula I, R^2 is $\text{C}(\text{O})\text{NH}_2$, 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 $\text{C}(\text{O})\text{NH}_2$, 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 $\text{C}(\text{O})\text{OEt}$, R^1 is SCH_3 ,
 10 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 $\text{N}(\text{C}(\text{O})\text{CH}_3)_2$, R^2 is $\text{CH}_2\text{Ph}(\text{p-Me}, \text{p-Cl})$, 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 $\text{N}(\text{C}(\text{O})\text{CH}_3)_2$, R^2 is
 15 $\text{CH}_2\text{Ph}(\text{p-OMe})$, 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 $\text{C}(\text{O})\text{NH}_2$, R^1 is CH_3 , R^3 is Ph, R^4 is CH_3 and R^5 is H;
- 20 (s) in a compound of formula I, R^2 is $\text{C}(\text{O})\text{NH}_2$, 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 $\text{C}(\text{O})\text{NH}_2$, R^1 is CH_3 , R^3 is m- CF_3Ph , 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
 25 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 $\text{CH}=\text{CH}-$
- 30 $\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{C}(\text{O})\text{O-iPr}$;
- (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 $\text{CH}=\text{CH}-$
 $\text{CH}(\text{OH})\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{C}(\text{O})\text{O-nPr}$;

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- (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- CF_3 -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;

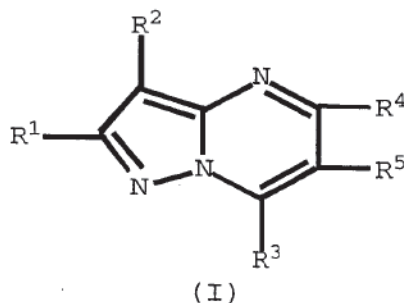
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- (rr) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is CH_3 , R^3 is $O-CL, m-Cl-Ph$, R^4 and R^5 are H ;
- (ss) in a compound of formula I, R^2 is $C(O)OMe$, R^1 is $-SCH_2-Ph$, R^3 is Ph, R^4 is Me and R^5 is H ;
- 5 (tt) in a compound of formula 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 ;
- 10 (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 ;
- 15 (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;
- 20 (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 ;
- 25 (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 ;
- 30 (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 ;

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- (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 ;
- 5 (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 ;
- 10 (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 ;
- 15 (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)NH₂, 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.
- 20

2. A compound of formula I:



25

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

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- R^1 is selected from the group consisting of
- C_{1-6} alkyl,
 - C_{2-10} alkenyl,
 - 5 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
 - 10 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 O or S(O)_n,
 - 15 wherein R¹ 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
- 20 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,
 - 25 C_{1-10} alkyloxy,
 - C_{1-10} alkyloxy C_{1-10} alkyl,
 - C_{1-4} alkoxy C_{1-4} alkyl,
 - SO₂- C_{1-10} alkyl
 - SO₂R^{2a} wherein R^{2a} is aryl,
 - 30 -SO₂R^{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)_n C_{1-4} alkyl, C(O)NR^{2c}R^{2d}, CO₂ C_{1-4} alkyl,
 - C_{3-8} cycloalkyl, C_{1-6} alkyloxy C_{1-6} alkyl, -C(O) C_{1-4} alkyl

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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;

5

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

10

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

-CN,

15

- $S(O)_n R^{2e}$ 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;

20

- $CO_2 R^{2f}$,

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

25

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

- $NR^{2g} CONR^{2f} R^{2h}$, 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;

30

- $NR^{2g} CO_2 R^{2e}$,

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

1-morpholinyl,

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- 1-piperidinyl,
 1-piperazinyl,
 and
 C_{3-8} cycloalkyl wherein 0-1 carbon atoms in the C_{4-8}
 5 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
 10 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
 15 substituted with 0-1 R^{21} and in which 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,
 20 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-
 25 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}
 30 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
 5 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, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$,
 10 $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ 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} ;

15 wherein

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

20 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, $R^{2q}S(O)_n-C_{1-4}$ alkyl and $R^{2r}R^{2s}N-C_{2-4}$ alkyl;

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl-
 25 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;

30

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 heteroaryl (C_{1-4} alkyl)-

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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;

5

$R^{2r}R^{2s}$ 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} ;

10

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);

15

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

aryl is selected from phenyl, naphthyl, indanyl and

20

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, $-CN$, $-NO_2$, $-SH$, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, -

25

$NR^{2q}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2q}CONR^{2o}R^{2p}$, $-NR^{2q}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ 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;

30

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

III

- 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 substituted 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,
- 15 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;
- 20 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, (C₁₋₄ alkyl)₂ amino and phenyl, each phenyl is substituted
- 25 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 (C₁₋₄ alkyl)₂ amino and wherein R^4 and R^5
- 30 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}

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alkyl(OH)_nCO₂R wherein R is H or C₁₋₆ alkyl, C₁₋₆ alkyl(OH)_n, wherein n is 0-3 or R⁴ and R⁵ may join together to form a C₃₋₆ alkylene chain.

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3. The compound according to Claim 1 or 2 wherein

R¹ is selected from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, -XR^{1c} wherein R¹ is substituted with
10 0-6 substituents selected from halogen, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

R² is selected from substituted-C₁₋₁₀ alkyl, branched C₃₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₈ cycloalkyl, C₃₋₆
15 cycloalkyl C₁₋₆ alkyl, -NR^{2c}R^{2d} wherein, in the case of substituted-C₁₋₁₀ alkyl, 1-3 substituents are independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br, Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl
20 which is substituted with 0-1 R²ⁱ and in which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O- and wherein the R² groups, other than substituted-C₁₋₁₀ alkyl, are substituted with 0-3 substituents independently selected from the group R²ⁱ, R^{2j}, R^{2k}, C₁₋₆ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, Br,
25 Cl, F, I, C₁₋₄ haloalkyl, -OR^{2g}, -NR^{2g}R^{2h}, -C₁₋₆ alkylOR^{2g}, and C₃₋₈ cycloalkyl which is substituted with 0-1 R²ⁱ and in which 0-1 carbons of C₄₋₈ cycloalkyl is replaced by -O-.

4. The compound according to Claims 1 or 2 or 3 wherein
30 R³ is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

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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;

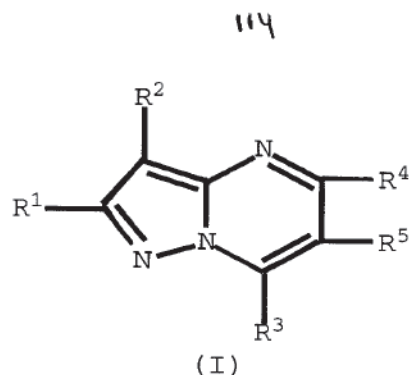
or R^2 is selected from $NR^{2c}R^{2d}$ wherein R^{2c} and R^{2d} are independently selected from H or C_{1-6} alkyl.

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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 substituted 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} .

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7. A compound of formula (I)



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

5

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

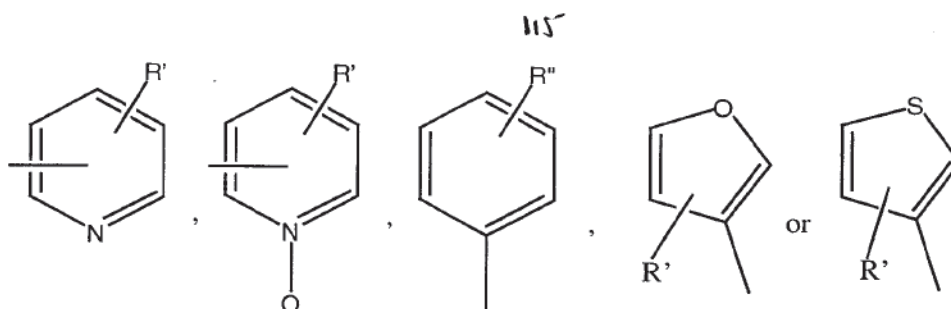
R^2 is selected from C_{1-4} alkyl which is unsubstituted or substituted with 1-4 substituents selected from C_{1-6}

10 alkyl, C_{3-8} cycloalkyl, C_{1-6} alkylOR^{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 , $S(O)_n C_{1-6}$ 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;

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

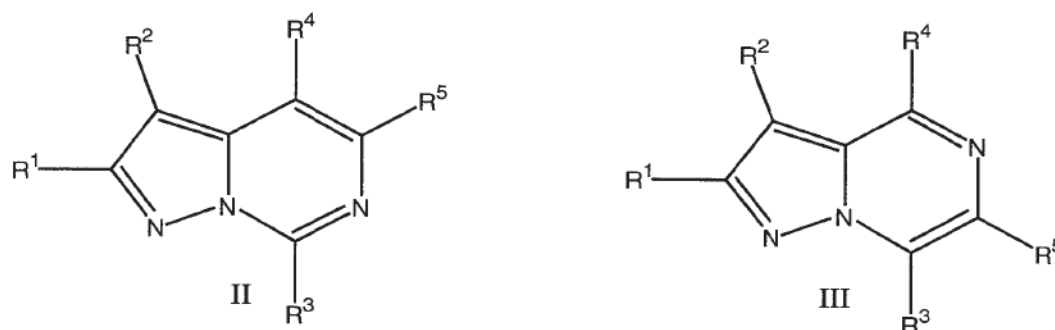
with the proviso that when R^1 and R^2 are unsubstituted, unbranched C_{1-3} alkyl, R^3 may not be



wherein R' is H or C₁₋₃ alkyl and R'' is H or o-
 5 trifluoromethyl, m-trifluoromethyl or m-methoxy.

8. The compound according to Claims 1-7 wherein R³ is substituted with 2-4 substituents.

10 9. A compound of the formula:



or a pharmaceutically acceptable salt or isomer thereof
 15 wherein R¹-R⁵ and other variables are as defined in claims 1-8.

10. Use of a compound according to Claims 1-9 in
 therapy.

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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

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis	Group Art Unit:	Not Yet Assigned
Serial Number:	US18/307,718	Examiner:	Not Yet Assigned
Filing or 371 (c) Date:	2023-04-26	CONFIRMATION NO:	9067
Title:	CORTICOTROPIN RELEASING FACTOR RECEPTOR ANTAGONISTS		

FILED ELECTRONICALLY ON: May 10, 2023

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 \$260.00 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 \$260.00 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(c) (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.
- 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 \$0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-709.307).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: May 10, 2023

By: /Stephen Olshemski/

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Pyrazolopyrimidines as CRF receptor antagonists

Abstract

translated from Japanese

(57) Abstract: The present invention relates to a compound of the formula (I) having CRF receptor antagonism. Wherein R^1 is NR^4R^5 or OR^5 ; R^2 is C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylthio; R^3 is hydrogen, C_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfoxy or C_{1-6} alkylthio; R^4 is hydrogen, C_{1-6} alkyl, mono- or di- (C_{3-6} cycloalkyl) methyl, R^5 is C_{3-6} cycloalkyl, C_{3-6} alkenyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyloxy C_{1-6} alkyl or C_{1-6} alkoxy C_{1-6} alkyl; C_{1-8} alkyl, mono- or di- (C_{3-6} cycloalkyl) methyl, Ar^1 CH_2 , C_{1-6} alkoxy C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{3-6} alkenyl, thienylmethyl, furanylmethyl, C_{1-6} alkylthio C_{1-6} alkyl, morpholinyl, mono or di- (C_{1-6} alkyl) amino C_{1-6} alkyl, di- (C_{1-6} alkyl) amino, C_{1-6} alkylcarbonyl C_{1-6} alkyl, C_{1-6} alkyl substituted with imidazolyl; or or an expression -Alk-O-CO-Ar¹ group; pyrrolidinyl which may be optionally substituted or R^4 and R^5 together with the nitrogen atom to which they are attached, piperidinyl, homopiperidinyl or a pharmaceutically acceptable acid addition salt form thereof; a pharmaceutical composition containing such a compound as an active ingredient; A method for treating disorders associated with hypersecretion of CRF, such as depression, anxiety, substance abuse, by administering an effective amount of a compound of formula (I).

Classifications

CO7D487/04 Ortho-condensed systems

View 29 more classifications

JP2000503661A

Janssen

English for All Similar

Other languages: Japanese

Inventor: チエン, チエン, ウェブ, トーマス・アール, マノカール, シェー, ジェイムズ・アール, セラン, テレンス・ジェイ, ウイル, コクセン, ケープ・エム, フラング, チャールズ

Current Assignee: Janssen Pharmaceutica NV

Worldwide applications

1997 EP CZ JP FI DE EA KR DK WO SA PT EE ES SK AG TR CN DE AT BR NZ IL HU TW AR ID 1998 BG NO 2001 JF

Application JP9528123A events

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2017-01-30 Anticipated expiration

Status Expired - Fee Related

Info: Patent citations (4), Cited by (56), Legal events, Similar documents, Priority and Related Applications

External links: Espacenet, Global Dossier, Discuss

Claims (1)

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[Claims] 1. Formula (I) [Where, R^1 is $NR^{Four}R^{Five}$ or OR^{Five} ; R^{Two} is C_{1-6} Alkyl, C_{1-6} Alkoxy or C_{1-6} Alkylthio; R^{Three} is hydrogen, C_{1-6} Alkyl, C_{1-6} Alkylsulfonyl, C_{1-6} Alkyl sulfoxide Si or C_{1-6} Alkylthio; R^{Four} is hydrogen, C_{1-6} Alkyl, mono- or di- (C_{3-6} Cycloalkyl) methyl, C_{3-6} Cycloalkyl, C_{3-6} Alkenyl, hydroxy C_{1-6} Alkyl, C_{1-6} Alkylcarbonyloxy C_{1-6} Alkyl or C_{1-6} Alkoxy C_{1-6} Alkyl is; R^{Five} is C_{1-6} Alkyl, mono- or di- (C_{3-6} Cycloalkyl) methyl, Ar^1 CH_2 , C_{3-6} Alkenyl, C_{1-6} Alkoxy C_{1-6} Alkyl, hydroxy C_{1-6} Alkyl, thienylmethyl, furanylmethyl, C_{1-6} Alkylthio C_{1-6} Alkyl, morpholinyl, mono- or di- (C_{1-6} Alkyl) amino C_{1-6} Alkyl, di- (C_{1-6} Alkyl) amino, C_{1-6} Alkylcarbonyl C_{1-6} Alkyl, imida C substituted with zolyt, C_{1-6} Alkyl, or a formula -Alk-O-CO-Ar¹ in the base of Or Or R^{Four} And R^{Five} Together with the nitrogen atom to which they are attached if necessary C_{1-6} Alkyl or C_{1-6} Alkoxy C_{1-6} Substituted with alkyl Pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl Can form a radical; Ar is phenyl; halo, C_{1-6} Alkyl, trifluoromethyl, hydroxy, Aro, C_{1-6} Alkoxy, benzyloxy, C_{1-6} Alkylthio, nitro, a Mino and mono- or di- (C_{1-6} Alkyl, independently selected from alkyl) amino, Phenyl substituted with 2 or 3 substituents; pyridinyl, halo, C_{1-6} Alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6} Alkoxy, benzyloxy, C_{1-6} Alkylthio, nitro, amino, mono- or di- (C_{1-6} Alkyl) 1, 2 or 3 positions independently selected from amino and piperidinyl A pyridinyl substituted with a substituent; said substituted phenyl is optionally substituted by one or more Can be further substituted with further halogens; Ar¹ is phenyl; halo, C_{1-6} Alkyl, C_{1-6} Alkoxy, di- (C_{1-6} Alkyl) amino C_{1-6} Substituted with alkyl, trifluoromethyl and morpholinyl C_{1-6} With one, two or three substituents each independently selected from alkyl Substituted phenyl; or pyridinyl; Alk is C_{1-6} Alkanediyl; However, 5-methyl-3-phenyl-7- (phenylmethoxy) -pyrazolo [1,5 -a] -pyrimidine and 2,5-dimethyl-7- (methylamino) -3-phenyl Le-pyrazolo [1,5-a] pyrimidine is not included). A compound comprising a sex and a pharmaceutically acceptable acid addition salt form. 2. R^1 is OR^{Five} And R^{Five} is C_{1-6} alkyl; or R^1 is $NR^{Four}R^{Five}$ And R^{Four} is hydrogen, C_{1-6} Alkyl, hydroxy C_{1-6} Alkyl, C_{1-6} Alkyl Carbonyloxy C_{1-6} Alkyl or C_{3-6} Alkenyl, R^{Five} is C_{1-6} Alkyl, C_{3-6} Alkenyl, hydroxy C_{1-6} Alkyl, C_{1-6} Alkoxy C_{1-6} Alkyl, phenylmethyl or C_{3-6} cycloalkylmethyl; or R^{Four} And R^{Five} Together with the nitrogen atom to which they are attached, C_{1-6} Alkyl or C_{1-6} Alkoxy C_{1-6} H. piperidinyl which can be substituted with alkyl Forming a dilyn, piperidinyl, homopiperidinyl or morpholinyl group, R^{Two} But C_{1-6} Alkyl, R^{Three} is hydrogen, C_{1-6} Alkyl or C_{1-6} Alkylthio Ar is halo, C_{1-6} Alkyl or C_{1-6} Independently selected from alkoxy A phenyl substituted with 1, 2 or 3 substituents; r is halo, amino, nitro, trifluoromethyl, mono- or di- (C_{1-6} Alkyl) amino, piperidinyl or C_{1-6} Each independently selected from alkyl Pyridinyl substituted with one, two or three substituents The compound according to claim 1. 3. R^1 is $NR^{Four}R^{Five}$ And R^{Four} is C_{2-4} Alkyl, hydroxy C_{1-2} Alkyl, C_{3-4} Alkenyl or C_{1-2} Alkylcarbonyloxy C_{2-4} Alkyl; R^{Five} But C_{2-4} Alkyl, C_{3-4} Alkenyl, hydroxy C_{2-4} Alkyl or cyclopropyl R methyl; R^{Two} is C_{1-2} Alkyl; R^{Three} is hydrogen, C_{1-2} Alkyl or C_{1-2} Is alkylthio The compound according to any one of claims 1 to 2. 4. R^1 is $NR^{Four}R^{Five}$ And R^{Four} is C_{3-4} Alkyl or allyl; R^{Five} is C_{2-4} Alkyl, allyl or cyclopropylmethyl; R^{Two} is methyl R^{Three} is methyl; Ar is halo, C_{1-6} Alkyl or C_{1-6} With

alkoxy Phenyl substituted at the 3-, 4-, 5-, 2,4- or 2,4,6-position is The compound according to any one of claims 1 to 3. 5. R¹ is NR^{Four}R^{Five} and R^{Four} is C₃₋₄Alkyl or allyl; R^{Five} is C₃₋₄Alkyl, allyl or cyclopropylmethyl; R^{Two} is methyl, R^{Three} is But Ar is methyl or dimethylamino in the 4- and / or 6-position Substituted 3-pyridinyl The compound according to any one of claims 1 to 3. 6. Compound 3-[6-(dimethylamino)-3-pyridinyl]-2,5-dimethyl-N, N-Dipropylpyrazolo [2,3-a] pyrimidin-7-amine; or 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-Tyl-N, N-Dipropylpyrazolo [2,3-a] pyrimidin-7-amine; Claims are their stereochemically isomeric forms or pharmaceutically acceptable acid addition salts 2. The compound according to item 1, wherein 7. Claims of a pharmaceutically acceptable carrier and a therapeutically effective amount of the active ingredient. A composition comprising the compound according to any one of items 1 to 6. 8. Pharmaceutical preparation of a compound according to any one of claims 1 to 6 in a therapeutically effective amount. Claim 7 characterized in that it is intimately mixed with a chemically acceptable carrier. Of the compositions described above. 9. A compound according to any one of claims 1 to 6 for use as a medicament. 10. Physiological conditions resulting from hypersecretion of corticotropin releasing factor (CRF) Or a compound for the manufacture of a medicament for the treatment of a disorder, 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo [1,5-a] pyrimidine and 2,5-Dimethyl-7-(methylamino)-3-phenyl-pyrazolo [1,5-a] pi R containing limidine¹, R^{Two}, R^{Three} And Ar are as defined in claim 1 Which includes its stereoisomers and pharmaceutically acceptable acid addition salt forms Use of compounds. 11. Formula (II') Wherein the group R^{Two}, R^{Three} And Ar are the same as defined in any of claims 1 to 5 W is hydroxy, halo, mesyloxy or tosyloxy; However, compounds in which Ar is unsubstituted phenyl are not included,] Or a stereoisomer or acid addition salt thereof. 12. a) The intermediate of the formula (ii) is reacted with the intermediate of the formula (iii) in a solvent inert to the reaction. And react withb) the intermediate of formula (vii) in a solvent inert to the reaction and in the presence of a suitable base O-alkylating the intermediate of formula (vi) using¹ is OR^{Five}OF formula (i) Can produce a compound of formula (Ia) defined as a compound, [In the above reaction formula, the group R¹, R^{Two}, R^{Three}, R^{Five} And Ar are in claim 1 As defined, W is a suitable leaving group; Alternatively, if desired, the compound of formula (i) can be converted to a compound of formula (i) known in the art. If necessary, further converting the compound of formula (i) with an acid. By conversion to an acid addition salt, or conversely, use an alkali to convert the acid addition salt form to an acid addition salt. By conversion to the free base; and, if desired, its stereochemical isomerism. Manufacture body morphology A method for producing the compound according to claim 1, wherein 13. The intermediate of formula (iv) is reacted with a β-ketoester (v) in a solvent inert to the reaction. Reacting, whereby W' is hydroxy, of the formula (ii') Giving a compound of formula (ii'-a) defined as a compound; [In the above reaction formula, the group R^{Two}, R^{Three} And Ar are the same as defined in claim 1. And W is hydroxy, halo, mesyloxy or tosyloxy. Optionally, a compound of formula (ii'-a) is substituted with a compound of formula (ii' wherein W is other than hydroxy. Or a compound of formula (ii'-b), defined as a compound of formula (ii). Alternatively, if desired, the compound of formula (ii') can be converted to a compound known in the art. Conversion to one another according to a rearrangement reaction; and optionally, a compound of formula (ii') Conversion to an acid addition salt by treatment with an acid or vice versa Conversion to the free base by treatment with lysate, and, if desired, its sterilization To produce isomeric forms A process for producing a compound of formula (ii') according to claim 10, characterized in that:

Description

translated from Japanese

DETAILED DESCRIPTION OF THE INVENTION Pyrazolopyrimidines as CRF receptor antagonists **Background of the Invention** The present invention relates to pyrazolopyrimidines having CRF receptor antagonistic activity, an active ingredient and Pharmaceutical compositions containing these compounds as well as generally stress-related disorders Its use in treating endocrine, psychiatric and neurological situations or diseases, including harm. About. The first corticotropin releasing factor (CRF) was isolated from sheep hypothalamus, identified as a 41-amino acid peptide (Vale et al., Science ce 213: 1394-197, 1981). Followed by human and rat CRF Sequence is isolated and identical to sheep CRF at 7 of 41 amino acid residues. (Rivier et al., Proc. Natl. Acad. Sci. USA 80: 4851, 1983; Shibahar. a et al., EMBO J. ; 2: 775, 1983). CRF is endocrine, it has been found to significantly alter the function of the nerves and the immune system. CRF is the adrenal gland Stimulating hormone ("ACTH"), β-endorphin and others from the anterior pituitary gland Pro-opiomelanocortin ("POMC")-derived peptides It is believed to be the major physiological modulator of res-release (Vale et al., Science 213: 1394-197, 1981). Briefly, CRF initiates its biological effects by binding to plasma membrane receptors Apparently, it is the brain (DeSouza et al., Science 221: 1449-1451, 1984), pituitary gland (DeSouza et al., Methods Enzym. ol. 124: 560, 1986; Wynn et al., Biochem. Biophys. Res. Comm. 110: 602-398, 1983), kidney (Udelman et al., Nature 319: 147-150, 1986) and tiles (Webster, EL, and EB DeSo). Uza, Endocrinology 122: 609-317, 1988) It has been found to be distributed throughout the body. CRF receptor is a GTP-binding protein (Perrin et al., Endocrinology. y 118: 1171-1179, 1986), which is responsible for the intracellular production of cAMP. Mediates increased CRF stimulation in (Bilezikjian, LM, and d W. W. Vale, Endocrinology 113: 657-662, 1983). In addition to its role in stimulating the production of ACTH and POMC, CRF Likely cooperate with many of the endocrine, autonomic and behavioral responses to And may be included in the pathophysiology of affective disorders. In addition, CRF is immune, central nervous, internal It appears to be a key intermediate in communication between lactation and the cardiovascular system (Croffond et al., J. et al. Clin. Invest. 90: 2555-2564, 1992; Sapolsky et al., Science 238: 522-524, 1987; Tiktors et al., Regul. Pep tides 5: 77-84, 1982). Overall, the CRF is an axis One of the trans-system neurotransmitters, it regulates the overall response of the body to stress Will play a decisive role in this case. Animals exposed to stressful environments when CRF is administered directly to the brain Elicits the same behavioral, physiological and endocrine responses as observed in For example, CR Intraventricular injection of F activates behavior (Sutton et al., Nature). 297: 331, 1982), permanent activation of EEG (Ehlers et al.), Brain Res. 2/8332, 1983), of the sympathetic adrenal medulla pathway. Stimulation (Brown et al., Endocrinology 110: 92) 8, 1982), increased heart rate and blood pressure (Fisher et al., End. ocrinology 110: 2222, 1982), increased oxygen consumption (B row et al., Life Science 30: 207, 1982.), Changes in gastrointestinal activity (Williams et al., Am. J. Physiol. ol. 253: G582, 1987), suppression of food consumption (Levine et al.) et al., Neuropharmacology 22: 337, 1983), gender. Transformation of Behavior (Srinathsinghi et al., Nature 305: 232, 1983) and the crisis of immune function (Irwin et al., Am. J. Physiol. 255: R744, 1988). More Floor data is available in the brain when CRF is depressed, anxiety-related disorders and anorexia nervosa. Has been shown to be hypersecreted (DeSouza, Ann. Reports in Med. Chem. 25: 215-223, 1990). Therefore, clinical data indicate that CRF receptor antagonists produce symptoms of CRF hypersecretion. Novel antidepressants and / or anti-cancer drugs that may be useful in the treatment of emerging neuropsychiatric disorders It indicates that it can be a cheap drug. CRF receptor Antagonists disclose, for example, substituted 4-thio-5 oxo-3-pyrazoline derivatives. U.S. Pat. No. 5,063,245 and substituted 2-aminothiazole derivatives Australian Patent No. AU-A-41399 / 93. WO-92 / 18504 and JP-32 / 04877 disclose pyrazo as an anti-inflammatory drug. B [1,5-a] pyrimidine is disclosed. WO-94 / 13676, WO- 94/13677 and WO-95 / 33750 are also CRF receptor antagonists Pymolopyrimidine, pyrazolo [3,4-d] pyrimidine and substituted purines are disclosed. Ing. Arylpyrazolo [1,5-a] pyrimidine inhibits xanthine oxidase Agents (Robins et al., J. Heterocycl. click Chem. 22: 601-634, 1985). JP-42 / 011, 753 are 7-methylamino pyrazolo [1,5 useful as sedatives and anti-inflammatory drugs -A] pyrimidine derivatives. And JP-61 / 057,587 Discloses pyrazolo [1,5-a] pyrimidine derivatives useful as anti-ulcer drugs. Has significant CRF receptor binding activity due to the physiological importance of CRF; Yet another biologically active small molecule capable of antagonizing the CRF receptor Development remains a desirable goal. One such CRF receptor antagonist is Endocrine, psychiatric and neurological conditions or diseases, generally including stress-related disorders Would be useful in the treatment of **Description of the invention** The present invention provides a compound comprising a stereoisomer and a pharmaceutically acceptable acid addition salt form. (i) [Where, R¹ is NR^{Four}R^{Five} Or OR^{Five} is; R^{Two} is C₁₋₆Alkyl, C₁₋₆Alkylalkoxy or C₁₋₆Alkylthio, R^{Three} is hydrogen, C₁₋₆Alkyl, C₁₋₆Alkylsulfonyl, C₁₋₆Alkyl sulfoxyl Si or C₁₋₆Alkylthio; R^{Four} is hydrogen, C₁₋₆Alkyl, mono- or di (C₃₋₆Cycloalkyl) methyl, C₃₋₆Cycloalkyl, C₃₋₆Alkenyl, hydroxy C₁₋₆Alkyl, C₁₋₆Alkylcarbonyloxy C₁₋₆Alkyl or C₁₋₆Alkylalkoxy C₁₋₆Alkyl is; R^{Five} is C₁₋₆Alkyl, mono- or di (C₃₋₆Cycloalkyl) methyl, Ar¹ CH₂WO, C₁₋₆Alkylalkoxy C₁₋₆Alkyl, hydroxy C₁₋₆Alkyl, C₃₋₆Alkenyl, thienylmethyl, furanyl methyl, C₁₋₆Alkylthio C₁₋₆Archi Morpholinyl, mono- or di (C₁₋₆Alkyl) amino C₁₋₆Alkyl, Di (C₁₋₆Alkyl) amino, C₁₋₆Alkylcarbonyl C₁₋₆Alkyl, imide C substituted with zely₁₋₆Alkyl, or a formula -Alk-O-CO-Ar³ In the base of Or Or R^{Four} And R^{Five} Together with the nitrogen atom to which they are attached C₁₋₆Alkyl or C₁₋₆Alkylalkoxy C₁₋₆May be substituted with alkyl Pyrrolidinyl, piperidinyl, homopiperidinyl Or a morpholinyl group can be formed; Ar is phenyl; halo, C₁₋₆Alkyl, trifluoromethyl, hydroxy, Ano, C₁₋₆Alkylalkoxy, benzyloxy, C₁₋₆Alkylthio, nitro, a Mino and mono- or di- (C₁₋₆1, independently selected from alkyl) amino, Phenyl substituted with 2 or 3 substituents; pyridinyl; halo, C₁₋₆Alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆Alkylalkoxy, ben Jiloxyl, C₁₋₆Alkylthio, nitro, amino, mono- or di (C₁₋₆Alkyl) 1, 2 or 3 positions independently selected from amino and

piperidiny A pyridinyl substituted with a substituent; said substituted phenyl is optionally substituted by one or more. Can be further substituted with further halogens; Ar¹ is phenyl; halo, C₁₋₆Alkyl, C₁₋₆Alkyl, di (C₁₋₆Alkyl) amino C₁₋₆Substituted with alkyl, trifluoromethyl and morpholino C₁₋₆With one, two or three substituents each independently selected from alkyl Substituted phenyl, or pyridinyl, Alk is C₁₋₆Alkanediyl CRF antagonist compounds. In yet another aspect, the present invention provides a novel compound of formula (I) as defined above. With the proviso that 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo [3,5-a] pyrimidine and 2,5-dimethyl-7-(methylamino)-3-Phenyl-pyrazolo [1,5-a] pyrimidine is not included. However, the writing is JP-61 / 057,587 and JP-42 / 011,7. 53 is intended to exclude the compounds disclosed. As used in the definitions above and below, halo is fluoro, chloro, bromo and And iodine. C₁₋₆Alkanediyl is a divalent linear group having 1 to 6 carbon atoms and branched saturated hydrocarbon groups such as methylene, 1,2-ethanediyl, 1,3-p-lopandiyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexyl C. defines sandiyl and their branched isomers; C₁₋₂Alkyl has 1 to 1 carbon atoms Two straight-chain saturated hydrocarbon radicals, such as methyl and ethyl; C₃₋₄Archi Are straight-chain and branched chain saturated hydrocarbon groups having 2 to 4 carbon atoms, for example, ethyl, Propyl, 1-methylethyl and the like; C₃₋₄Alkyl has 3 to 4 carbon atoms Linear and branched saturated hydrocarbon groups such as propyl, butyl, 1-methylethyl, Etc.; C₁₋₆Alkyl is C as defined above. C₃₋₆Alkyl and C₃₋₆A Alkyl groups and their higher homologues having 5 to 6 carbon atoms, such as pentyl, pen including tyl, hexyl and hexyl isomers: C₁₋₆Archi is C₁₋₆Archi And their higher homologs having 7 to 8 carbon atoms, such as heptyl and octyl. Including: C₃₋₆Alkenyl is a straight chain containing one double bond and having 3 to 6 carbon atoms. And branched hydrocarbon groups such as 2-propenyl, 3-butenyl, 2-pentene N, 3-pentenyl, 3-methyl-2-butenyl and the like; C₃₋₆Al When kenyl is attached to nitrogen or oxygen, the carbon atoms forming the bond are saturated Is preferred. C₃₋₆Cycloalkyl is cyclopropyl, cyclobutyl, cyclobutyl includes cyclopentyl and cyclohexyl. Hydroxy C₁₋₆Alkyl is hydroxy C substituted with a sil-group; C₆Say alkyl. Homopiperidiny is one nitrogen source Refers to a 7-membered saturated ring containing a child. Depending on the nature of some of the substituents, the compound of formula (I) may have one or more. Can contain asymmetric centers, which use the commonly used R and S nomenclature Can be referred to. The compounds of the present invention contain a basic nitrogen atom and can be used as such in the form of a free base. Can exist in the form of acid addition salts, both of which are part of the present invention. Acid addition Salts can be prepared by methods well known in the art and include organic and inorganic salts. It can be formed from acids. Suitable organic acids include maleic acid, fumaric acid, benzoic acid, succinic, succinic, methanesulfonic, acetic, oxalic, propyl On-acid, tartaric acid, salicylic acid, citric acid, gluconic acid, lactic acid, mandelic acid, itic acid, aspartic acid, stearic acid, palmitic acid, glycolic acid, glutu includes formic acid and benzenesulfonic acid. Suitable inorganic acids are hydrochloric acid, hydrobromic acid, Sulfuric acid, phosphoric acid and nitric acid. Certain groups of compounds within the scope of the invention are subject to one or more of the following limitations. Is a compound of formula (I): a) R¹ is NR^{Four}R^{Five}Where R^{Four}is hydrogen, C₁₋₆Alkyl, hydroxy C₁₋₆Alkyl, C₁₋₆Alkylcarbonyloxy C₁₋₆Alkyl or C₃₋₆Alkenyl Especially C₂₋₄Alkyl, hydroxy C₁₋₂Alkyl C₃₋₄Alkenyl or C₁₋₂A Alkylcarbonyloxy C₂₋₄Alkyl, R^{Five}is C₁₋₆Alkyl, C₃₋₆Al Kenyl, hydroxy C₁₋₆Alkyl, C₁₋₆Alkyl C₁₋₆Alkyl, Fe Nilmethyl or C₃₋₆Cycloalkylmethyl, especially C₂₋₄Alkyl, C₃₋₆Arche Nil, hydroxy C₂₋₄Alkyl or cyclopropylmethyl; b) R¹ is OR^{Five}Where R^{Five}is C₁₋₆Alkyl, especially C₂₋₄Archi Is c) R^{Two}is C₁₋₆Alkyl, especially C₁₋₂is alkyl; d) R^{Three}is hydrogen, C₁₋₆Alkyl or C₁₋₆Alkylthio; especially hydrogen, C₁₋₂Archi Or C₁₋₂Alkylthio; e) Ar is C₁₋₆Alkyl, C₁₋₆Each independently from alkoxy or halo Phenyl substituted with one, two or three substituents of choice; The nyl moiety is preferably in the 3-, 4-, 6-, 2,4- or 2,4,6-position Substituted; or Ar is halo, amino, nitro, trifluoromethyl, Mono- or di (C₁₋₆Alkyl) amino, piperidiny or C₁₋₆Alkyl Pyridinyl substituted with 1, 2 or 3 substituents each independently selected from Where the pyridinyl moiety is preferably the molecule via the 2- or 3-position is bound to the rest. Another specific group of compounds are represented by R¹ is NR^{Four}R^{Five}And R^{Four}And R^{Five}Are they combined Together with the nitrogen atom. C₆Alkyl or C₁₋₆Alkyl Kishi C₁₋₆Pyrolidiny, piperidiny which can be substituted with alkyl, A compound of formula (I) forming a homopiperidiny or morpholino group.

Preferred compounds are R¹ is NR^{Four}R^{Five}And R^{Four}is C₃₋₆Alkyl or alkyl, preferably Preferably propyl; R^{Five}is C₂₋₄Alkyl, alkyl or cyclopropylmethyl R, preferably propyl; R^{Two}is methyl, R^{Three}is hydrogen, methyl or methyl Aryl is halo, methyl or methoxy. Phenyl substituted with 1, 2 or 3 substituents each independently selected Ar is particularly halo, 1, 2 or 3 positions independently selected from tyl or dimethylamino A compound of formula (I) which is pyridinyl substituted with a substituent. Ar is substituted at the 4- and / or 6-position with methyl or dimethylamino More preferably, it is 3-pyridinyl. Most preferred 3-(2,4-dichlorophenyl)-5-methyl-7-(N-propyl-N-cyclopropanemethylamino)-pyrazolo [2,3-a] pyrimidine; 3-(2,4-dichlorophenyl)-5-methyl-7-(N-allyl-N-cyclopropanemethylamino)-pyrazolo [2,3-a] pyrimidine; 2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N,N-diallylamino)-pyrazolo [2,3-a] pyrimidine; 2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-Butyl-N-cyclopropanemethylamino) pyrazolo [2,3-a] pyrimidine; 2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-Propyl-N-cyclopropanemethylamino) pyrazolo [2,3-a] pyrimidin N; 2-methyl-3-(4-chlorophenyl)-5-methyl-7-(N,N-dipropylamino) pyrazolo [2,3-a] pyrimidine; 3-[6-(dimethylamino)-3-pyridinyl]-2,5-dimethyl-N,N-Dipropylpyrazolo [2,3-a] pyrimidin-7-amine; or 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-Ty-N,N-Dipropylpyrazolo [2,3-a] pyrimidin-7-amine; Is 3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(N-propyl-N-methoxyethylamino)-pyrazolo [2,3-a] pyrimidine; Stereoisomers and pharmaceutically acceptable acid addition salts thereof A compound selected from The compounds of the present invention generally comprise a pyrazolopyrimidine of formula (II) And alkylation using an intermediate of the formula (1). Intermediate (I In I). W is halo, for example a chloro, bromo or sulfonyloxy group, A suitable leaving group such as, for example, a mesyloxy or tosyloxy group. The above reaction is typically carried out in a suitable solvent such as an aprotic solvent such as DMF or in acetonitrile, ethers such as tetrahydrofuran, preferably high At room temperature and if the intermediate of formula (III) is a volatile amine, it is done in a bottle. R represented by the formula (Ia)¹ is OR^{Five}is a compound of formula (VI)) Using an intermediate of formula (VI) wherein W is as defined above it can also be produced by O-alkylation. Wear: The reaction for the preparation of the compounds of the formula (Ia) is carried out in a solvent inert to the reaction, for example N 2 The presence of a suitable base, such as sodium hydride, in N, N dimethylformamide Below, preferably at a temperature in the range between room temperature and reflux temperature. R represented by the formula (Ic)¹ is NR^{Four}R^{Five}is a compound of formula (V) From any of the compounds of (II) or (IX), a suitable N-By alkylation reaction, wherein W is as defined above it is. These N-alkylations are carried out in solvents inert to the reaction, for example tetrahydrofuran. Performed in ethers such as orchids, preferably in the presence of strong bases such as NaH It is. In some cases the reaction is R^{Two}is (R^{Four}Or R^{Five}) Alkylated by -W. Especially R^{Two}is methyl and R^{Four}Or R^{Five}is C₁₋₆Can produce by-products that are alkyl. As outlined below, compounds of formula (I) are known in the art. Can be converted into each other according to the conversion method. R^{Three}is C₁₋₆Compounds of formula (I) which are alkylthio may be oxidized, for example dichloro Peroxides such as 3-chloroperbenzoic acid in a solvent inert to a reaction such as methane By processing using R^{Three}is C₁₋₆Alkylsulfonyl or C₁₋₆Alkyl sulfoxyl it can be converted to a compound of formula (I) which is The amount of oxidizer and other reaction parameters By controlling the parameters, R^{Three}is C₁₋₆Alkylsulfonyl or C₁₋₆A Obtaining a mixture of either or both of the compounds of formula (I) which are alkylsulfoxyl. The mixture can then be subjected to conventional methods, e.g., column chromatography. Can be more separated. Compounds of formula (I) may be prepared via reactions or functional group transformations known in the art. They can be converted to each other. For example, hydroxy C₁₋₆Formula having an alkyl group (The compound of I) is placed in a solvent inert to the reaction, for example dichloromethane, for example. Treatment with an acid anhydride, optionally in the presence of a base such as pyridine, C₁₋₆Alkylcarbonyloxy C₁₋₆Conversion to compounds of formula (I) having an alkyl group can do. A compound of formula (I) having a nitro group is converted to a compound of formula (I) having an amino group. And then mono- or di (C₁₋₆Alkyl) amino groups of the formula (I) Can be converted to a compound. Conversion of amino group to halo using diazotization reaction You can also. In addition, the Ar group of the compound of formula (I) is halogenated in a suitable solvent, such as acetic acid. Can be halogenated with an agent such as chlorine or bromine, optionally The reaction can be carried out at a temperature in the range between room temperature and the reflux temperature of the reaction mixture. Intermediates of formula (II) are described in Robins et al., J. et al. Heterocyclic Chem. 22: 607-634, 1985 Can be manufactured. The aminopyrazole derivative (IV) is preferably used under reflux conditions and THF as an example. React with β-ketoester (V) in a solvent inert to a suitable reaction such as To give

hydroxypyrazolopyrimidine (VI), for example, by converting (VI) to methane Sulfonyloxychloride or halogenating agent such as POCl₃. Processing by Converts the hydroxy group of intermediate (VI) to a leaving group W by the formula (II'). The intermediate of formula (VIII) can be obtained by treating the intermediate of formula (II) with ammonia. Manufactured. In one embodiment, the present invention also provides an intermediate of formula (II'), wherein W' Represents hydroxy, halo, mesyloxy or tosyloxy. However, Ar is other than phenyl. The intermediate of formula (II') is prepared according to the method used for the preparation of the intermediate of formula (II). Wherein W' is hydroxy A compound of formula (II'-a) defined as a compound of (II') is obtained. Optionally, a compound of formula (II'-a) is substituted with a compound of formula (II' wherein W' is other than hydroxy.) To a compound of formula (II'-b) defined as a compound of formula (II'-b). Stereoisomers may be prepared according to methods known in the art, for example, optically active acids. And the resulting diastereoisomeric salt is selectively crystallized or separation of the final product of formula (I) by separation by column chromatography It can be manufactured by separation. Alternatively, the starting material, which is a stereoisomer, either of the proposed or used in the preparation of the intermediates described below isomers can be prepared. The efficacy of a compound as a CRF receptor antagonist can be determined by various assays Can be determined. Suitable CRF antagonists of the present invention include their receptors for CRF. And can antagonize the activity associated with CRF. Wear: DeSouza et al. (J. Neuroscience 7: 88, 1987) and Battaglia et al. (Synapse 1: 572, 1987), but not limited to No), generally accepted for the purpose of evaluation for activity as a CRF antagonist The compound of formula (I) can be converted to CRF by one or more assays It can be evaluated for activity as an antagonist. As mentioned above, a suitable CRF Antagonists include compounds that exhibit CRF receptor affinity. CRF receptor affinity is a radiolabeled CRF (eg, [¹²⁵I] Tyrosine CRF) receptor (eg Receptor prepared from rat cerebral cortical membrane. —) can be determined by binding studies that measure the ability of a compound to inhibit binding to it can. DeSouza et al. (ibid., 1987). A radioligand binding assay determines the affinity of a compound for the CRF receptor. Provides an assay to determine. Such activities are typically associated with radiolabeled ligase. IC₅₀ as the concentration of compound required to remove 50% of the compound from the receptor₅₀Or is calculated from the following equation: $K_d \frac{[L]}{[R]}$ Where L = radioligand, K_d = The affinity of the radioligand for the receptor (Cheng and d Prusoff, Biochem. Pharmacol. 22: 3099, 1973) In addition to inhibiting CRF receptor binding, compounds Anti-drug activity can be established by the ability of the compound to antagonize the activity associated with CRF, example CRF stimulates various biochemical processes, including adenylate cyclase activity It is known to Therefore, for example, by measuring the amount of cAMP, Compound by its ability to antagonize CRF-stimulated adenylate cyclase activity It can be evaluated as an antagonist. Battaglia et al. (Same as above, 1987), a CRF-stimulated adenylate cyclase activity assay. Say provides an assay to determine the ability of a compound to antagonize CRF activity. Therefore, in general, the initial binding assay (DeSouza (Id., 1987)) (As disclosed) and subsequently a proposed cAMP screening (Battaglia (as disclosed by id., 1987). CRF receptor antagonist Anti-drug activity can be determined. Referring to the CRF receptor binding affinity, The CRF receptor antagonist of the present invention has 10 μM Having. Preferred of the present invention in a preferred embodiment, the CRF receptor antagonist is less than 1 μM, and more preferably K less than 0.25 μM (ie, 250 nM) Having. The CRF receptor antagonist of the present invention exhibits activity at the CRF receptor site. Treatment of a wide range of disorders, including endocrine, psychiatric and neurological disorders or diseases. Can be used as a therapeutic agent for More specifically, the CRF receptor of the present invention Ter antagonists are useful in treating physiological conditions or disorders arising from hypersecretion of CRF. Can be useful. CRF is endocrine, behavioral and automatic against stress Because it appears to be a pivotal neurotransmitter that activates and coordinates the sexual response, the present invention CRF receptor antagonists can be used to treat neuropsychiatric disorders. Of the present invention Neuropsychiatric disorders that can be treated with CRF receptor antagonists include affective disorders, Eg depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder; threatening disorder Abnormal attacks, neurovascular abnormalities such as unstable angina and reactive hypertension; Eating disorders include, for example, anorexia nervosa, bulimia and irritable bowel syndrome. CRF antagonists treat stress-induced immunosuppression and seizures with various disease states May also be useful. Other uses for the CRF antagonists of the invention include inflammatory conditions Rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and I. Mobility etc.) , Cushing's disease, convulsions, epilepsy and convulsions in both infants and adults And treatment of various substance abuse and withdrawal symptoms (including alcoholism) You. In another embodiment of the present invention, one or more CRF receptor antagonists Disclosed are pharmaceutical compositions containing For the purpose of administration, the compound of the invention It can be prepared as a pharmaceutical composition. The pharmaceutical composition of the present invention CRF receptor antagonists (ie, compounds of structure (I)) and pharmaceutically acceptable Carrier and / or diluent. CRF receptor antagonists may A therapeutically effective amount, ie, sufficient to achieve CRF receptor antagonist activity. in the composition, and preferably in an amount that is acceptable for the patient. Exist. The pharmaceutical composition of the present invention preferably comprises a CRF receptor antagonist administered. 0.1 mg to 250 mg, more preferably 1 mg to 5 mg per dose depending on the route It can be included in an amount of 0 mg. Suitable concentrations and dosages are known in the art. It can be easily determined by a skilled person. Pharmaceutically acceptable carriers and / or diluents are those skilled in the art. Well known to For compositions prepared as liquid solutions, acceptable Body and / or diluents include saline and sterile water, optionally containing antioxidants, implants, bacteriostats and other conventional additives may be included. Pills, capsules, granules The compositions may also be prepared as agents or tablets, which are antagonists of the CRF receptor It contains, in addition to the drug, diluents, dispersants and surfactants, binders and lubricants. Those skilled in the art will further appreciate in a suitable manner and in Remington's s Pharmaceutical Science, Gennaro, Ed., Mack Publishing Co., Easton, USA, 1990. CRF receptor according to accepted practices such as those disclosed in -Antagonists can be prepared. In another embodiment, the invention relates to endocrine, psychiatric and neurological disorders or Methods are provided for the treatment of a variety of disorders or diseases, including diseases. Such a way Requires administering the compound of the present invention to a warm blooded animal in an amount sufficient for treating a disorder or disease. Including. Such a method is preferably carried out in the form of a pharmaceutical composition. Includes systemic administration of RF receptor antagonists. As used herein, systemic Administration includes oral and parenteral administration. CRF receptor for oral administration Suitable pharmaceutical compositions of antagonists include powders, granules, pills, tablets and capsules. Liquids, syrups, suspensions and emulsions. These compositions are used for flavoring. Also includes preservatives, suspending, thickening and emulsifying agents and other pharmaceutically acceptable additives be able to. For parenteral administration, the compounds of the invention may be formulated as aqueous solutions for injection. It can be prepared by adding buffer, antioxidant in addition to CRF receptor antagonist Agents, bacteriostats and other additives commonly used in such solutions. Wear. As noted above, administration of the compounds of the invention may be used to treat a variety of disorders or diseases. Can be. Especially depression, anxiety disorder, panic disorder, threatening disorder, abnormal attack, instability Angina, reactive hypertension, anorexia nervosa, bulimia, irritable bowel syndrome, stress -induced immunosuppression, seizures, inflammation, Cushing's disease, convulsive seizures, epilepsy and substances The compounds of the invention can be administered to warm-blooded animals for the treatment of abuse or withdrawal symptoms. Wear. Thus, the present invention results from hypersecretion of corticotropin releasing factor (CRF) Use of a compound of formula (I) for the manufacture of a medicament for the treatment of a physiological condition or disorder. In a further embodiment, a novel compound of formula (I) as a medicament Provide use of The following examples are provided by way of illustration, not limitation. **Experimental part** In the following, "THF" means tetrahydrofuran and "DCM" is It means dichloromethane. **A. Production of intermediates Example A.1 a)** 3-Amino-4- (2,4-dichlorophenyl) pyrazole and acetoacetic acid Ethyl (2 equiv) was dissolved in dioxane and heated under reflux overnight. True mixture Concentrated in air and diluted with ethyl acetate. Off-white produced after standing for 2 days The solid was collected by vacuum filtration and the 3- (2,4-dichlorophenyl) -5-methyl Cyl-7-hydroxypyrazolo [2,3-a] pyrimidine (intermediate 1) was obtained. b) intermediate 1 (300 mg) THF (1.5 ml) and heat for 1 hour Refluxed. The resulting purple solution was carefully transferred into ice-water. The product is treated with ethyl acetate Extracted with saturated sodium bicarbonate and brine, washed with MgSO₄, Dry on And concentrated in vacuo to give 3- (2,4-dichlorophenyl) -5-methyl-7-chloro Lopyrazolo [2,3-a] pyrimidine (intermediate 2) was obtained as a brown solid (2.60 mg, 82%). **Example A.2 a)** Stirring of sodium hydride (60%, 25 mmol) in THF (10 ml) The solution was added to 6- (dimethylamino) -3-pyridineacetone in THF (10 ml). Tolyf (10 mmol) was added dropwise. The solution was stirred for 10 minutes before ethyl acetate ((30 mmol) was added slowly. The resulting suspension is stirred at room temperature for another hour. Was. The reaction mixture is concentrated under vacuum, Dissolved in ethyl acetate / methanol (1: 1) and filtered through silica. The filtrate was concentrated to obtain (intermediate 7) b) Mixture of intermediate 7 and hydrazine hydrobromide (100 mmol) with ethanol Dissolved in knol / water (9: 1, total 100 ml) and refluxed for 1 hour. Reaction mixing The material was concentrated and the residue was partitioned between ethyl acetate and sodium bicarbonate solution. Matching The extract was dried over sodium sulfate, filtered and concentrated to dryness. 1,4 residue -Dissolved in dioxane (200 ml) and in the presence of ethyl acetate for 16 hours Refluxed. The reaction mixture was cooled and an off-white

solid precipitated. Crystallization Diethyl ether was added to help, the precipitate was filtered, dried and 3-[2-(di-methylamino)-5-pyridinyl]-2,5-dimethyl-7-hydroxypyrazolo [2,3-a] Pyrimidine (intermediate 8) was obtained. c) converting intermediate 8 to POCH₃ (2 ml) and refluxed for 2 hours. Reaction mixture Was cooled and poured on ice. Make the solution basic by adding solid sodium carbonate (F+H = 9) and extracted with diethyl ether. Combine the organic layers with sodium sulfate, filtered, concentrated and concentrated to give 3-[5-(dimethylamino)-3-pyridyl]-Nyl-2,5-dimethyl-7-chloro-pyrazolo [2,3-a] pyrimidine (intermediate 9) was obtained. Table 1 lists intermediates made according to one of the above examples. **B. Production of final products Embodiment B.1** Intermediate 2 (21 mg) and N-propyl-N-cyclopropanemethylamine (75 mg) was heated in a sealed reaction bottle at 100 ° C. overnight. Chromatography on a preparative TLC plate using 1:5 ethyl acetate-hexane 3-(2,4-dichlorophenyl)-5-methyl-7-(N-propyl-N-cyclopropanemethylamino)-pyrazolo [2,3-a] pyrimidine (compound 17) (17.4 mg) and 3-(2,4-dichlorophenyl)-5-methyl-7-(N-cyclopropanemethylamino)-pyrazolo [2,3-a] pyrimidine (compound 18) (1 mg) got it. in a similar manner, intermediate 2 and (S)-(-)-leucic acid and (Starting from R)-(+)-leucic acid, (S)-2-[3-(2,4-dichloro) Rophenyl]-5-methyl-7-pyrazolo [2,3-a] pyrimidinyl amino]-4-Methyl-1-pentanol (Compound 11) and its R analog (Compound 12) was produced. **Embodiment B.2** Intermediate 10 (8 g) and di-n-propyl alcohol in acetonitrile (50 ml) A solution of the min (13 g) was heated at reflux for 3 hours. Mix the mixture with ethyl acetate filter through a Picalgel stopper and concentrate the filtrate in vacuo to give a light yellow solid, which is Recrystallization from ether-hexane gave 8.9 g (93%) of 3-[6-(dimethyl)-Amino]-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo [2,3-a] pyrimidin-7-amine (Compound 53) was obtained. Conversion Compound 53 (8.1 g) was added to diethyl ether (150 ml) and DCM (50 ml). And HCl in diethyl ether (1M, 21.3 ml) was dissolved in Compound 53 is treated by treating the mixture by dropwise addition with stirring. The hydrochloric acid addition salt was also converted. The resulting off-white solid was collected by filtration. 8.7 g (98%) of 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo [2,3-a] pyrimidin-7-amine monohydrochloride was obtained. **Embodiment B.3** Intermediate 3 (15 mg) was dissolved in ethanol (0.5 ml), stirred in the presence of lithium ethoxide (12 mg) for 1 hour. Chromium on silica gel The chromatography was 3-(2,4-dichlorophenyl)-7-(ethoxy)-5-Methyl-2-methylthio-pyrazolo [2,3-a] pyrimidine (compound 50) Gave **Embodiment B.4** A solution of compound 6 (14 mg) in THF (3 ml) was treated with sodium hydride at room temperature. Treatment with lithium (60 mg, excess) for 5 minutes followed by iodopropane (0.3 ml). The reaction was stirred overnight at room temperature and quenched with methanol (0.5 ml). Ching. The resulting mixture was loaded onto a preparative TLC plate and 1:5 ethyl acetate-Expanded with hexane to give 3-(2,4-dichlorophenyl)-5-methyl-7-[N-(3-methoxypropyl)-N-propylamino]-Pyrazolo [2,3-a] pyrimidine (compound 45) (5.7 mg), 3-(2,4-dichlorophenyl)-5-buty-7-[N-(3-methoxypropyl)-N-propylamino]-pyrazolo [2,3-a] pyrimidine (compound 46) (4 mg) and 3-(2,4-dichlorophenyl)-5-buty-7-[3-methoxy O-propylamino]-pyrazolo [2,3-a] pyrimidine (compound 47) (3.5 mg). **Embodiment B.5** Compound 26 (8 mg) was dissolved in DCM (1 ml) and acetic anhydride (0.1 ml) and Pyridine (0.1 ml). The mixture is stirred overnight at room temperature and And concentrated. Dilute the residue with ethyl acetate and filter through a short silica gel column did. The filtrate was concentrated to give 3-(2,4-dichlorophenyl)-5-methyl-7-[N-(2-acetoxyethyl)-N-Benzylamino]-pyrazolo [2,3-a] pyrimidine (compound 27) (8.5 mg) as a colorless oil. **Embodiment B.6** A solution of compound 40 (20 mg) in DCM (3 ml) was treated with 3-chloroperbenzoic acid (19 mg). The solution was stirred at room temperature for 1 hour. Ethyl acetate-hexane Chromatography on a silica gel plate using (1:1) gave compound 43 and the compound Object 44 was given **Embodiment B.7** Compound 55, palladium on activated carbon (10 ml) in dry ethanol (100 ml) 0 mg) of the mixture was charged to the hydrogenation apparatus and 2.7 10⁶ Pa (40 psi) For 2 hours. The reaction mixture was filtered and concentrated. Diethyl residue Dissolved in toluene, concentrated and concentrated to 1.49 g of 3-(5-amino-3-methyl-2-pyridinyl)-2,5-dimethyl-N,N-dipropylpyrazolo [2,3-a] Pyrimidin-7-amine (Compound 56) was obtained. **Embodiment B.8** Compound 56 (1.39 g) and aqueous formaldehyde in ACN (20 ml) (5.4 g) to a stirred solution of sodium cyanoborohydride (743 mg) at 0 ° C. Added in Glacial acetic acid (1 ml) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. Organic layer Wash with brine, dry over sodium sulfate, filter, concentrate to dryness and remove silica gel. Column chromatography (CH₂Cl₂/CH₂OH/ NH₄OH/ O H 150: 10: 1). The desired fraction was isolated and 1.30 g of 3-[5-(Dimethylamino)-3-methyl-2-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo [2,3-a] pyrimidin-7-amine (compound 57) Got **Embodiment B.9** Compound in a mixture of concentrated HCl (1 ml) and water (1 ml) cooled in an ice bath To a solution of 56 (100 mg) of sodium nitrite (21 mg) in water (1 ml) The solution was added. The solution was added to a mixture of copper (I) chloride (281 mg) in conc. It was added with stirring in the bath. Heat the solids and mixture to be separated to 50 ° C. A solution was obtained. The reaction mixture was basified with NaOH and extracted with ethyl acetate, Washed with brine and concentrated. Purification by preparative TLC yielded 16 mg of compound 98. Gave **Embodiment B.10** Compounded with a solution of fluoroboric acid (48% by weight in water, 2 ml) cooled in an ice bath Material 56 (100 mg) was added, followed by sodium nitrite (20 ml) in water (1 ml). mg). The temperature was kept below 10 ° C. The solid is collected by filtration, Dry and partition between aqueous sodium bicarbonate and ethyl acetate. Organic layer with brine Wash, concentrate and purify the residue by preparative TLC to give 20 mg of compound 100 I got Tables 2-5 list compounds made according to one of the above examples and Table 6 And 7 list analytical data for these compounds. **C. Pharmacological examples Example C.1 Representative compound having CRF receptor binding activity.** DeSouza et al. (J. Neurosci. 7: 88-100, 1987), in a standard radioligand binding assay. Compounds were more evaluated for binding activity to the CRF receptor Various radioactive markers By using a CRF ligand, one of the compounds of the invention can be assayed using an assay. The binding activity to these CRF receptor subtypes can also be evaluated. simply in other words, the binding assay removes radiolabeled CRF ligand from CRF receptors. Including leaving. More specifically, the binding assay was performed in a 1.5 ml Eppendorf tube. In the tube, the human CRF receptor was stably transfected. About 1x10⁶ This was performed using individual cells. Label each tube with unlabeled saquinavir about 0.1 ml of assay buffer (eg. Dul becco's phosphate buffered saline, 10 mM magnesium chloride, 20 µM bacit Lassin), urotensin I for determination of non-specific binding I) or CRF (final concentration, 1 µM), 0.1 ml [¹²⁵I] Tyrosine-H Azalea CRF (final concentration, about 200 pM or determined by Scatchard analysis Approximate K_D) And 0.1 ml of the cell suspension containing the CRF receptor The liquid was put. The mixture was incubated at 22 ° C. for 2 hours, followed by binding by centrifugation and Free radioligand was separated. After washing the pellet twice, the tube is Cut immediately above and monitored with gamma counter for radioactivity at approximately 80% efficiency. Non-linear least squares-fitting of all radioligand binding data Analyzed using the program. Binding activity is the activity of the radiolabeled ligand from the receptor. Corresponds to the concentration (nM) of compound required to remove 50%. The following compounds are K_iWith ± 250 nM: 5, 10, 12, 15 to 15 listed in Tables 2 to 5 17, 19, 23, 24, 26, 27, 29, 31 to 33, 36 to 43, 48, 49, 51-54 and 57-130. Compounds 17, 29, 38, 41, 42, 48, 49, 51 to 54, 57, 58, 70, 71, 81 to 85, 90 to 92, 101, 103-105, 115, 118, 121-123 and 125 Was found to show the highest score. **Example C.2 CRF-stimulated adenylate cyclase activity** The compounds of the present invention can also be evaluated by various functional tests. For example a book Screen compounds of the invention for CRF-stimulated adenylate cyclase activity can do. An assay for determining CRF-stimulated adenylate cyclase activity Say, with modifications to adapt the assay to whole cell samples, Battaghi et al. (Synapse 1: 572, 1987). You can do it exactly as it appears. More specifically, the standard assay mixture Can contain the following in a final volume of 0.5 ml: in DMEM buffer With 2 mM L-glutamine, 20 mM HEPES and 1 mM IBMX. stimulation In the study, all cells with the transfected CRF receptor Were plated in 24-well plates and various concentrations of CRF-related and non- Incubate with related peptides for 1 hour at 37 ° C. Establish a pharmacological ranking profile for the ter subtype. For incubation Subsequently, the medium is aspirated, the wells are gently rinsed once with fresh medium and the medium is aspirated. For determination of the amount of intracellular cAMP 300 µl of a solution of 95% ethanol and And a 20 mM aqueous hydrochloric acid solution were added to each well, and the resulting suspension was heated at -20 ° C. for 16 to 16 hours. incubate for 18 hours. Put the solution in a 1.5 ml Eppendorf tube And wash the wells with an additional 200 µl of an aqueous ethanol / hydrochloric acid solution. Pool with fractions. The sample is lyophilized and then 500 µl of sodium acetate Resuspend with buffer solution. Measurement of cAMP in sample requires one antibody kit Perform using Causes 80% stimulation of cAMP production for functional evaluation of compounds One concentration of CRF or a related peptide can be combined with various concentrations of competitor compound (10⁻¹² ~ 10⁻⁶ Incubate with M). **Example C.3** Plus-maze and defensive withdrawal (defens) paradigms are examples of experimental treatments. An exploratory activity phase sensitive to anxiogenic and anxiolytic effects it is a Seki scale. Using these animal models, the anti-anxiety and anti- The stress effect was investigated. **Example C.3.a. elevated plus-maze example** This test involves an approach involving a brightly lit space versus a dark "safe" area- Move to avoid-avoidance situation Predict how things will react. Both spaces are raised high and off the ground And constitutes two lanes that intersect in the form of a plus sign. Of this type The approach-avoidance situation is a classic test of "emotional" and responsiveness, with a desuppressant (sedative And / or stress-treating treatments). No motivation is required, and animals remain in the dark or are released at risk. You are free to appear on the arm. The plus-maze device has four arms at right angles to each other (10 x 50 cm) and raised above the floor (80 cm). Arm 2 One is walled (40 cm high) and the two arms have no walls (open arms). Suffered Test animals are individually placed in the center of the

maze and have free access to all four arms for 5 minutes. You are allowed to. Test animals are placed through a door window and on a computer monitor. Observed via an on-line display of the rat's location. Spend on each arm. Recorded time is automatically recorded by photoelectric cell beam and computer program is done. During each test, the maze is wiped clean with a damp cloth. This mission (The measure of anxiety-like behavior at task) is the time spent on the open arm. And the measure of anti-stress efficiency is the complement of the time spent on the open arm. It is an increase. The plus-maze legitimacy using the CRF peptide: Exposure to central administration of CRF and any of several experimental stressors suppress exploration in anxiety elevated plus maze models. Action against social defeat. If the response is measured after the stress- [25 µg ICV] or before the stress- [1 µg ICV] alpha-helix CRF (9-41). Central administration of antagonists reverses the anxiogenic effects of social defeat. The anti-stress effect of this CRF antagonist is exerted even after intracerebral administration into the central nucleus of the amygdala. [250 µg ICV]. One hour before the 5 minute test, rats were dosed orally with test compound. A few Groups were placed in a water-filled pool for 90 seconds immediately before being placed in the plus-maze. Tress group, standard test animals were removed directly from their home cage (non-stress group). For untreated animal groups, the percentage of average time spent in the open arm was observed (from about 36 to about 16%). 2.5 or 20 mg / kg of compound 53, the % time in the open arm is within the error range for the untreated group. Returned to an equal level within. Example C. 3.b. Defensive withdrawal paradigm The test was a galvanized cylinder 17.1 cm deep and 10.2 cm in diameter. This is done in an open area of plexiglass containing a steel chamber. Chamber are open at one end, lined up and open along the walls of the open space. It is placed 15.0 cm away from the corner of the field. The open end faces the corner. The open area is illuminated by fluorescent ceiling lights. For testing, the animals are introduced them into an unfamiliar test environment by placing them in a chamber. Persistent for exam it takes 5 minutes and after each test the device is cleaned with a dilute acetic acid solution. Trial The test compound is administered orally 1 hour before the 5 minute test. Animal Behavior Video Monitored and recorded by the camera. Latency to leave the chamber is Everything is measured and defined as being placed in open space. Chamber and open space Number of passes between chambers and chambers per entry. The average length of time inside is also measured. Measure of anxiety efficiency is enclosed chamber. The reduction in the average time spent within. Compound 53 has 0.63, 2.5 and When administered orally to rats at a dose of 20 mg / kg, the mean time in the chamber. The time is reduced from about 80 seconds to about 20-40 seconds. Justification of defensive withdrawal using CRF peptide. When injected with ICV, both alpha-helical CRF (9-41) and CRF. They alter the behavior in the defensive withdrawal paradigm. In particular, make sure ICV administration of CRF in a lethal animal until exit from the small chamber increases both latency and average time spent in the chamber over a 15 minute period. Let it. Similarly, infusion of CRF into the locus is similar in defensive withdrawal behavior. Changes in CRF and noradrenergic neurons in rats in the defensive withdrawal behavior in Japan. Conversely, competitive CRF-receptor antagonist alpha-helix CRF (9-14) or d-Phe ICV administration of CRF (12-41) is an inhibitory stress in familiar environmental conditions. Reversing the CRF-like effect of air, latency to emerge in animals accustomed to the device And significantly reduce the average time measurement in the chamber. D. Composition examples The following preparations are suitable for systemic or local administration to warm-blooded animals according to the invention. 1 illustrates a typical pharmaceutical composition in unit form. Through these examples The "active ingredient" (A) used is a compound of formula (I), its N-oxide Form, pharmaceutically acceptable acid or salt. It relates to a group addition salt or a stereochemical isomer. Example D. 1. Oral solution 9 g of methyl 4-hydroxybenzoate and 1 g of 4-hydroxybenzoic acid pro. The pill is dissolved in 41 boiling purified waters. First add 10 g of 2,3-Dihydroxybutanedioic acid and then 20 g of A. I. Dissolve. The latter solution Combine with the rest of the former solution and combine 1,1,2,3-propanetriol and 121 And a 70% solution of sorbitol in 31 are added thereto. 40g saccharin sodium Dissolve the solution in 0.51 water, add 2 ml of raspberry essence and 2 ml of goose Add berry essence. Sufficient to combine the latter solution with the former to give 201 Water and add 5 mg of A.P./asp. 1. Oral solution containing Gel. The resulting solution is filled into a suitable container. Example D. 2. Capsule 20 g of A. I. 6 g sodium lauryl sulfate, 5g starch, 5g Lactose, 0.8 g colloidal silicon dioxide and 1.2 g mug stearate. The nesum is stirred vigorously with the former. The resulting mixture is subsequently diluted to 1000 suitable Filled into hardened gelatin capsules, each containing 20 mg of A.D. I. including. Example D. 3. Film-coated tablets. Tablet core manufacturing 100 g of A. I. A mixture of 570 g of lactose and 200 g of starch And then 5 g of sodium dodecyl sulfate in about 200 ml of water and 1 g Humidify with a solution of 0 g of polyvinylpyrrolidone. Sieve wet powder mixture, dry And sift again. Then there is 100g fine Microcrystalline cellulose and 15 g of hydrogenated vegetable oil are added. Mix the whole well, tablets To give 10,000 tablets, each containing 10 mg of active ingredient. coating 150 ml of a solution of 10 g of methylcellulose in 75 ml of denatured ethanol A solution of 5 g of ethyl cellulose in dichloromethane is added. Then there 7 Add 5 ml of dichloromethane and 2.5 ml of 1,2,3-propanetriol. I can. Melt 10 g of polyethylene glycol into 75 ml of dichloromethane Dissolve. The latter solution is added to the former, followed by 2.5 g of magnesium octadecanoate. Um, 5 g of polyvinylpyrrolidone and 30 ml of the deep colorant suspension were added. Uniform. Using the mixture obtained in this way, tablets Coat the core. Example D. 4. Solution for injection 1.8 g of methyl 4-hydroxybenzoate and 0.2 g of 4-hydroxybenzoic Propyl perate was dissolved in about 0.51 boiling water for injection. After cooling to about 50 ° C, 4 g of lactic acid, 0.05 g of propylene glycol and 4 g of A. I. Do not stir I added it. Cool the solution to room temperature and supplement with enough water for injection to make up 1 liter volume And 4 mg / ml of A. I. Was obtained. The solution is sterilized by filtration and has a sterile volume. The vessel was filled. Example D. 5. Suppository 3 grams of A. I. 3 grams in 25 ml polyethylene glycol 400 Was dissolved in a solution of 2,3-dihydroxybutanedioic acid. 12 grams of surfactant And 300 grams of triglyceride were melted together. The latter mixture was mixed well with the former solution. The resulting mixture is 37- Pour into molds at a temperature of 38 ° C, each with 30 mg / ml of A. I. 1 containing 60 suppositories were formed.

[Procedure of Amendment] Article 184-8, Paragraph 1 of the Patent Act [Submission date] November 14, 1997 (November 14, 1997) [Correction contents] In yet another aspect, the present invention provides a novel compound of formula (I) as defined above. With the proviso that 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo [2,3-a] -pyrimidine and 2,5-dimethyl-7-(methylamino)-3-Phenyl-pyrazolo [2,3-a] pyrimidine is not included. However, the writing is open to JP-61 / 057,587 and JP-42 / 011,753. It is intended to exclude the compounds shown. Halo, as used above and below, is defined as fluoro, chloro, bromo including molybdenum and iodine; C₁₋₆Alkanediyl is a divalent linear chain having 1 to 6 carbon atoms. And branched saturated hydrocarbon groups such as methylene, 1,2-ethanediyl, 1,3-Propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-Hexanediyl and its branched isomers; C₁₋₂Alkyl has carbon number 1 to 2 straight-chain saturated hydrocarbon radicals, such as methyl and ethyl; C₃₋₄Alkyl is a linear or branched saturated hydrocarbon group having 2 to 4 carbon atoms, for example, ethyl, Propyl, 1-methylethyl and the like; C₃₋₄Alkyl has 3-4 carbon atoms Linear and branched saturated hydrocarbon groups such as propyl, butyl, 1-methyl Ethyl and the like; C₁₋₆Alkyl is C as defined above. C₁₋₂Alkyl and C₃₋₄Alkyl groups and their higher homologs having 5 to 6 carbon atoms, such as pentyl, including pentyl isomers, hexyl and hexyl isomers; C₁₋₆Alkyl is C₁₋₆A Alkyl and their higher homologs having 7 to 8 carbon atoms, such as heptyl, octyl including; C₃₋₆Alkenyl is a straight chain containing one double bond and having 3 to 6 carbon atoms. Linear and branched hydrocarbon groups such as 2-propenyl, 3-butenyl, 2-Pentenyl, 3-pentenyl, 3-methyl-2-butenyl and the like; C₃₋₆Arche When nit is attached to nitrogen or oxygen, the carbon atom forming the bond is saturated. Preferably, C₃₋₆Cycloalkyl is cyclopropyl, cyclobutyl, cycloalkyl including lopentyl and cyclohexyl. Hydroxy C₁₋₆Alkyl is hydroxy C-substituted with C₁₋₆Say alkyl. Homopiperidiny has one nitrogen atom And a 7-membered saturated ring containing. Depending on the nature of some of the substituents, the compound of formula (I) may have one or more Which can contain the commonly used R and S nomenclature Can be used. The compounds of the present invention contain a basic nitrogen atom and can be used as such in the form of a free base. Can exist in the form of acid addition salts, both of which are part of the present invention. The aminopyrazole derivative (IV) is preferably used under reflux conditions and THF as an example. React with β-ketone (V) in a solvent inert to a suitable reaction such as To give hydroxypyrazolopyrimidine (VI), for example, by converting (VI) to methane Sulfonyloxichloride or halogenating agent such as POCl₃ in THF. Processing by Converts the hydroxy group of intermediate (VII) to a leaving group W by the formula (II). The intermediate of formula (VIII) can be obtained by treating the intermediate of formula (II) with ammonia. Manufactured. In one embodiment, the present invention also provides an intermediate of formula (II'), wherein W Represents hydroxy, halo, mesyloxy or tosyloxy. However, when Ar is other than phenyl or W is hydroxy or chloro, Other than 4-chlorophenyl, 4-fluorophenyl or 3-methylphenyl. The intermediate of formula (II') is prepared according to the method used for the preparation of the intermediate of formula (II). Wherein the compound of formula (II') wherein W is hydroxy Obtaining a compound of formula (II'-a), defined as: Optionally, a compound of formula (II'-a) is substituted with a compound of formula (II' wherein W is other than hydroxy,) To a compound of formula (II'-b) defined as a compound of formula (II'-b). Stereoisomers may be prepared according to methods known in the art, for example, optically active acids. And the resulting diastereoisomeric salt is selectively crystallized or Separation of the final product of formula (I) by separation by column chromatography It can be manufactured by separation. Alternatively, the starting material, which is a stereoisomer, Either of the

proposed or used in the preparation of the intermediates described below. Isomers can be prepared. However, 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo [2,3-a] -pyrimidine and 2,5-dimethyl-7-(methylamino)-3-phenyl-pyrazolo [2,3-a] pyrimidine is not included. Compound. 2. R¹ is OR^{Five} And R^{Five} is C₁₋₆ alkyl; or R¹ is NR^{Four} R^{Five} And R^{Four} is hydrogen, C₁₋₆ alkyl, hydroxy C₁₋₆ alkyl, C₁₋₆ alkyl carbonyloxy C₁₋₆ alkyl or C₃₋₆ alkenyl, R^{Five} is C₁₋₆ alkyl i.e. C₃₋₆ alkenyl, hydroxy C₁₋₆ alkyl, C₁₋₆ alkyloxy C₁₋₆ alkyl, phenylmethyl or C₃₋₆ is cycloalkylmethyl; or R^{Four} And R^{Five} Together with the nitrogen atom to which they are attached, C₁₋₆ alkyl or C₁₋₆ alkyloxy C₁₋₆ alkyl, pyridyl which can be substituted with alkyl forming a danyl, piperidinyl, homopiperidinyl or morpholinyl group; R^{Two} But C₁₋₆ alkyl, R^{Three} is hydrogen, C₁₋₆ alkyl or C₁₋₆ alkylthio Ar is halo, C₁₋₆ alkyl or C₁₋₆ independently selected from alkyloxy A phenyl substituted with 1, 2 or 3 substituents; r is halo, amino, nitro, trifluoromethyl, mono- or di (C₁₋₆ alkyl) amino, piperidinyl or C₁₋₆ Each independently selected from alkyl Pyridinyl substituted with one, two or three substituents The compound according to claim 1. 3. R¹ is NR^{Four} R^{Five} And R^{Four} is C₂₋₄ alkyl, hydroxy C₁₋₂ alkyl, C₃₋₄ alkenyl or C₁₋₂ alkyloxy carbonyloxy C₂₋₄ alkyl; R^{Five} But C₂₋₄ alkyl, C₃₋₄ alkenyl, hydroxy C₂₋₄ alkyl or cyclopropylmethyl; R^{Two} is C₁₋₂ alkyl, R^{Three} But Hydrogen, C₁₋₂ alkyl or C₁₋₂ is alkylthio The compound according to any one of claims 1 to 2. 4. R¹ is NR^{Four} R^{Five} And R^{Four} is C₃₋₆ alkyl or alkyl; R^{Five} is C₂₋₄ alkyl, alkyl or cyclopropylmethyl; R^{Two} is methyl; R^{Three} But Methyl; Ar is halo, C₁₋₆ alkyl or C₁₋₆ 3-4 in alkyloxy Phenyl substituted at the, 6-, 2, 4- or 2, 4, 6-position The compound according to any one of claims 1 to 3. 5. R¹ is NR^{Four} R^{Five} And R^{Four} is C₃₋₆ alkyl or alkyl; R^{Five} is C₃₋₄ alkyl, alkyl or cyclopropylmethyl; R^{Two} is methyl; R^{Three} But Ar is methyl or dimethylamino in the 4- and / or 6-position Substituted 3-pyridinyl The compound according to any one of claims 1 to 3. 6. Compound 3-[6-(dimethylamino)-3-pyridinyl]-2,5-dimethyl-N,N-Dipropylpyrazolo [2,3-a] pyrimidin-7-amine; or 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-Tyln, N-dipropylpyrazolo [2,3-a] pyrimidin-7-amine; Claims are their stereochemically isomeric forms or pharmaceutically acceptable acid addition salts 2. The compound according to item 1, wherein 7. Pharmaceutically acceptable carriers and active ingredients in therapeutically effective amounts A composition comprising the compound according to any one of claims 1 to 6. 8. Pharmaceutical preparation of a compound according to any one of claims 1 to 6 in a therapeutically effective amount. Claim 7 characterized in that it is intimately mixed with a chemically acceptable carrier. Of the compositions described above. 9. A compound according to any one of claims 1 to 6 for use as a medicament. 10. Physiological conditions resulting from hypersecretion of corticotropin releasing factor (CRF) Or a compound for the manufacture of a medicament for the treatment of a disorder, 5-methyl-3-phenyl-7-(phenylmethoxy)-pyrazolo [2,3-a] -pyrimidine and 2,5-Dimethyl-7-(methylamino)-3-phenyl-pyrazolo [2,3-a] p; R containing limidine¹, R^{Two}, R^{Three} And Ar are as defined in claim 1 Which includes its stereoisomers and pharmaceutically acceptable acid addition salt forms Use of compounds 11. Formula (II') Wherein the group R^{Two}, R^{Three} And Ar are the same as defined in any of claims 1 to 5 W is hydroxy, halo, mesyloxy or tosyloxy, Provided that compounds in which Ar is unsubstituted phenyl and W is hydroxy or chloro If Ar is 4-chlorophenyl, 4-fluorophenyl or 3-methylphenyl is not included.) Or a stereoisomer or acid addition salt thereof. 12. a) The intermediate of the formula (II) is reacted with the intermediate of the formula (III) in a solvent inert to the reaction. And react with b) the intermediate of formula (VII) in a solvent inert to the reaction and in the presence of a suitable base O-alkylating the intermediate of formula (VI) using¹ is OR^{Five} Of formula (I) To give a compound of formula (Ia) defined as a compound, [in the above reaction formula, the group R¹, R^{Two}, R^{Three}, R^{Five} And Ar are in claim 1 As defined, W is a suitable leaving group]; Alternatively, if desired, the compound of formula (I) can be converted to a compound of formula (I) known in the art. If necessary, further converting the compound of formula (I) with an acid. By conversion to an acid addition salt, or conversely, use an alkali to convert the acid addition salt form to an acid addition salt. To the free base by treatment with If desired, produce its stereochemically isomeric form A method for producing the compound according to claim 1, wherein 13. The intermediate of formula (IV) is reacted with a β-ketoester (V) in a solvent inert to the reaction. Reacting, thereby defining a compound of formula (II') wherein W is hydroxy To give a compound of formula (II'a)

-----続 8 Continued on the front page (51) Int.Cl. 7 Identification symbol FI theme coat¹
(Reference) A61P 25/24 A61K 31/00 B26L 25/22 B26K 25/08 B26B 25/30 B26P 29/00 B29 43 / B06430 A61K 31/519 31/505 B06 31/55 31/55 (81) Designated country
EP (AT, BE, CH, DE, DK, ES, FI, FR, GE, GR, IE, IT, LU, MC, NL, PT, SE), OA (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), AP (KE, LS, MW, SD, SZ, UG), UA (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), AL, AM, AU, BA, BB, BG, BR, CA, CN, C, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN (72) Inventor Chien, Chien 92121 1102, California, California, USA San Diego Science Parkload 3050 Neurocrine Biosciences Inc. (72) Invention Web, Thomas Earl 92121-1102, San Diego, CA, USA San Diego Science Park Road 3050 Neurocrine Biosciences, Inc. (72) Inventor Matsui Kirshi, J. Aima Earl 92121-1102, San Diego Science Park, CA, USA Load 3050 / Neurocrine Biosciences Incorporated (72) Inventor Moran, Terrence Jay 92121 1102, California, California, USA San Diego Science Parkload 3050 Neurocrine Biosciences Incorporated (72) Inventors Wilcoxon, Keith Em 92121 1102, San Diego, CA, USA San Diego Science Parkload 3050 Neurocrine Biosciences, Inc. (72) Inventor Huang, Charles, USA 92129, CA, United States San Diego Goldfish Court 12341

Patent Citations (4)

Publication number	Priority date	Publication date	Assignee	Title
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JPS6157587A *	1984-08-29	1986-03-24	Shionogi & Co Ltd	Condensed heterocyclic derivative and antiulcerative
JPH0087591B2 *	1988-06-29	1993-12-17	Surface High Performance Res	
TW444018B *	1992-12-17	2001-07-01	Pfizer	Pyrazolopyrimidines

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Publication number	Priority date	Publication date	Assignee	Title
JP2007507446A *	2003-10-03	2007-03-29	エフ・ホフマン・ラ・ロシュ アーゲー	Pyrazolo and imidazo-pyrimidine derivatives
JP2007515472A *	2003-12-22	2007-06-14	エスビー・ファルムコ・ブエ ルト・リコ・インコーポレイ テッド	CRF receptor antagonists and methods related thereto

JP2008503444A *	2004-02-13	2008-02-07	エスビー・ファルムコ・ブエルト・リコ・インコーポレイテッド	CRF receptor antagonist, its preparation, its pharmaceutical composition and its use
JP2008533201A *	2005-03-21	2008-08-21	イーライ リリー アンド カンパニー	Imidazopyridazine compounds
JP2009051643A *	2001-04-27	2009-03-12	Eisai R & D Management Co. Ltd.	PYRAZOLO[1,5-a]PYRIDINE COMPOUND AND ITS MEDICINE
JP2010504344A *	2006-09-20	2010-02-12	イーライ リリー アンド カンパニー	Thiazolopyrazolopyrimidines as CRF1 receptor antagonists
US8431603B2	2008-04-15	2013-04-30	Eisai R&D Management Co., Ltd.	3-phenylpyrazolo[5,1-b]thiazole compounds
US8530504B2	2009-10-06	2013-09-10	Eisai R&D Management Co., Ltd.	Pyrazolothiazole compound
JP202050832A *	2017-08-14	2020-10-29	スブールス バイオサイエンス インコーポレイテッド	Corticotropin-releasing factor receptor antagonist
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US6313124B1	1997-07-23	2001-11-06	Dupont Pharmaceuticals Company	Tetrazine bicyclo compounds
US6060478A *	1996-07-24	2000-05-09	Dupont Pharmaceuticals	Azolo triazines and pyrimidines
AT375344T *	1996-07-24	2007-10-15	Bristol Myers Squibb Pharma Co.	AZOLOTRIAZINE AND PYRIMIDINE
US7094782B1	1996-07-24	2006-08-22	Bristol-Myers Squibb Company	Azolo triazines and pyrimidines
AU709203B2	1996-08-06	1999-08-26	Pfizer Inc.	Substituted pyrido- or pyrimido-containing 5,6- or 6,7-bicyclic derivatives
US5723608A	1996-12-31	1998-03-03	Neurogen Corporation	3-aryl substituted pyrazolo 4,3-dipyrimidine derivatives; corticotropin-releasing factor receptor (CRF1) specific ligands
CA2281525A1	1997-02-18	1998-08-20	Neurocrine Biosciences, Inc.	Biazacyclic crf antagonists
CA2291709A1 *	1997-05-30	1998-12-03	Merck & Co., Inc.	Novel angiogenesis inhibitors
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AU748818C *	1998-01-28	2003-11-20	Du Pont Pharmaceuticals Company	Azolo triazines and pyrimidines
AU293109A	1998-03-06	1999-09-23	Janssen Pharmaceutica N.V.	Crf antagonistic pyrazolo[4,3-b]pyridines
US6472402B1	1998-04-02	2002-10-29	Neurogen Corporation	Aminoalkyl substituted 5,6,7,8-Tetrahydro-9H-Pyridino [2,3-B]indole derivatives
CA2326319A1	1998-04-02	1999-10-14	Neurogen Corporation	Aminoalkyl substituted 5,6,7,8-tetrahydro 9h pyrimidino[2,3-b]indole and 5,6,7,8-tetrahydro-9h-pyrimidino[4,5-b]indole derivatives; crf1 specific ligands
CA2359041A1 *	1999-01-29	2000-08-03	Sumitomo Chemical Co., Ltd.	Fat accumulation inhibitory agents
AU2331500A	1999-04-06	2000-10-23	Du Pont Pharmaceuticals Company	Pyrazolotriazines as crf antagonists
WO200005908A2	1999-04-06	2000-10-12	Du Pont Pharmaceuticals Company	Pyrazolopyrimidines as crf antagonists
US6432569B1	1999-08-27	2002-08-13	Pfizer Inc	Use of CRF antagonists to treat circadian rhythm disorders
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005271670A1	1999-10-29	2003-04-30	Pfizer Prod Inc	ANTAGONISTS OF THE CORTICOTROPINE RELEASE FACTOR AND RELATED COMPOSITIONS
TW271406B	1999-12-13	2007-01-21	Eisai Co Ltd	Tricyclic condensed heterocyclic compounds, preparation method of the same and pharmaceuticals comprising the same
AU2001232271A1 *	2000-02-14	2001-08-20	Japan Tobacco Inc.	Preventives/remedies for postoperative stress
JP2004531475A *	2001-01-26	2004-10-14	ブリストル-マイヤーズ スク イブ カンパニー	Imidazolyl derivatives as corticotropin releasing factor inhibitors
TW312347B	2001-02-08	2009-07-21	Eisai R&D Man Co Ltd	Bicyclic nitrogen-containing condensed ring compounds
US6872827B2	2002-04-26	2005-03-29	Chembridge Research Laboratories, Inc.	Somatostatin analogue compounds
US7161003B1 *	2002-09-04	2007-01-09	Schering Corporation	Pyrazolopyrimidines as cyclin dependent kinase inhibitors
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US7176216B2	2002-10-22	2007-02-13	Eisai Co., Ltd.	7-phenylpyrazolopyridine compounds
ES2295816T3	2003-01-14	2008-04-16	Arena Pharmaceuticals, Inc.	ARILO AND HETEROARILO 1,2,3-TRISUBSTITUTED DERIVATIVES AS METABOLISM MODULATORS, AND PROPHYLAXIS AND TREATMENT OF DISORDERS RELATED TO THE SAME, SUCH AS DIABETES AND HYPERGLUCEMIA.
EP1608552A1 *	2003-03-31	2005-12-28	Vernalis (Cambridge) Limited	Pyrazolopyrimidine compounds and their use in medicine
AR045047A1	2003-07-11	2005-10-12	Arena Pharm Inc	ARILO AND HETEROARILO DERIVATIVES TRISUBSTITUTED AS MODULATORS OF METABOLISM AND PROPHYLAXIS AND TREATMENT OF DISORDERS RELATED TO THEMSELVES
BR20060018A *	2003-07-14	2007-12-31	Arena Pharmaceuticals Inc.,	Fused-aryl and heteroaryl derivatives as modulators of metabolism and the prophylaxis and treatment of disorders related thereto
WO2005063756A1 *	2003-12-22	2005-07-14	Sb Pharmco Puerto Rico Inc	Crf receptor antagonists and methods relating thereto
GB0519957D0	2005-09-30	2005-11-09	Sb Pharmco Inc	Chemical compound
AT512966T	2005-02-11	2011-07-15	Hoffmann La Roche	PYRAZOLO PYRIMIDINE DERIVATIVES AS MGLUR2 ANTAGONISTS
CN101180299B	2005-03-23	2010-12-15	弗哈夫曼-拉罗切有限公司	Acetylenyl-pyrazolo pyrimidine derivatives as MGLUR2 antagonists
US7557103B2	2005-04-05	2009-07-07	Eli Lilly And Company	Imidazopyridazine compounds
WO2007017678A1 *	2005-08-09	2007-02-15	Elrx Therapeutics Limited	Pyrazolo[1,5-a] pyrimidine compounds and pharmaceutical compositions containing them
DE602006013493D1	2005-09-27	2010-05-20	Hoffmann La Roche	OXADIAZOLYL PYRAZOLOPYRIMIDINES AS MGLUR2 ANTAGONISTS
ES2428543T3 *	2006-09-20	2013-11-08	Eli Lilly And Company	Thiophenepyrzolo pyrimidine Compounds
EA201000128A1	2007-07-26	2010-08-30	Hoechst Ar	ORGANIC COMPOUNDS
WO2011204027A1	2010-09-22	2012-03-29	Arena Pharmaceuticals, Inc.	Modulators of the gp119 receptor and the treatment of disorders related thereto
GB201210686D0	2012-06-15	2012-08-01	Holsboemaschmeyer Neurochemie GmbH	V1B receptor antagonist for use in the treatment of patients having an elevated AVP level and/or an elevated copeptin level
GB201310782D0	2013-06-17	2013-07-31	Max Planck Innovation GmbH	Method for predicting a treatment response to a CRHR1 antagonist and/or V1B antagonist in a patient with depressive and/or anxiety symptoms
CN107405332A	2015-01-06	2017-11-28	艾尼纳制药有限公司	Treatment and S1P1 The method of receptor related illness
PL235355B1 *	2015-04-02	2021-01-11	Celon Pharma Spolka Akcyjna	Derivatives of 7-(morpholin-4-yl)pyrazolo[1,5-a]pyrimidine as inhibitors of kinase P13

* Cited by examiner, † Cited by third party, ‡ Family to family citation

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Publication	Publication Date	Title
JP2000503661A	2000-03-28	Pyrazolopyrimidines as CRF receptor antagonists
US6872998B1	2002-03-05	CRF receptor antagonists and methods relating thereto
US20060278659A1	2006-11-30	Pyrazolopyrimidines as CRF receptor antagonists

US6288319B1	2001-07-03	Thiophenopyrimidines
EP1344779B1	2005-08-10	Azolo-pyrimidines
JP2002529465A	2002-09-10	CRF receptor antagonists and methods for CRF receptor antagonists
US6734185B2	2004-05-11	Pyrolo[3,4-d]pyrimidines as corticotropin releasing factor (CRF) antagonists
US7094782B1	2006-08-22	Azolo triazines and pyrimidines
IL123835A	2006-09-05	3 - ARYL - 5, 7 - DISUBSTITUTED PYRAZOLO [1,5-a] - PYRIMIDINE DERIVATIVES, THEIR USE AS CRF RECEPTOR ANTAGONIST, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM
MXPA96009167A	1999-07-06	Pyrazolopyrimidines with antagonist properties of the corticotropin release factor receptor (crf) and pharmaceutical compositions that contain them
AU769402B2	2004-01-22	Biaxacyclic CRF antagonists

Priority And Related Applications

Child Applications (1)

Application	Priority date	Filing date	Relation	Title
JP2001255611A	1996-02-07	2001-09-03	Division	Pyrazolopyrimidine

Applications Claiming Priority (5)

Application	Filing date	Title
US1127996P	1996-02-07	
US60/011,279	1996-02-07	
US2768896P	1996-10-08	
US60/027,688	1996-10-08	
PCT/EP1997/000459	1997-01-30	Pyrazolopyrimidines as crf receptor antagonists

Legal Events

Date	Code	Title	Description
2005-06-28	S111	Request for change of ownership or part of ownership	Free format text: JAPANESE INTERMEDIATE CODE: R313113
2005-07-12	R360	Written notification for declining of transfer of rights	Free format text: JAPANESE INTERMEDIATE CODE: R360
2005-08-29	R370	Written measure of declining of transfer procedure	Free format text: JAPANESE INTERMEDIATE CODE: R370
2005-10-25	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2006-07-11	S111	Request for change of ownership or part of ownership	Free format text: JAPANESE INTERMEDIATE CODE: R313117
2006-07-29	R360	Written notification for declining of transfer of rights	Free format text: JAPANESE INTERMEDIATE CODE: R360
2006-09-04	R370	Written measure of declining of transfer procedure	Free format text: JAPANESE INTERMEDIATE CODE: R370
2006-10-24	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2007-10-23	FPAY	Renewal fee payment (event date is renewal date of database)	Free format text: PAYMENT UNTIL: 20081004 Year of fee payment: 6
2008-10-21	FPAY	Renewal fee payment (event date is renewal date of database)	Free format text: PAYMENT UNTIL: 20091004 Year of fee payment: 7
2009-10-01	FPAY	Renewal fee payment (event date is renewal date of database)	Free format text: PAYMENT UNTIL: 20091004

Year of fee payment: 7			
2009-10-05	FPAY	Renewal fee payment (event date is renewal date of database)	Free format text: PAYMENT UNTIL: 20101004 Year of fee payment: 8
2010-10-05	FPAY	Renewal fee payment (event date is renewal date of database)	Free format text: PAYMENT UNTIL: 20111004 Year of fee payment: 9
2011-10-04	FPAY	Renewal fee payment (event date is renewal date of database)	Free format text: PAYMENT UNTIL: 20121004 Year of fee payment: 10
2012-10-02	FPAY	Renewal fee payment (event date is renewal date of database)	Free format text: PAYMENT UNTIL: 20131004 Year of fee payment: 11
2013-10-04	LAPS	Cancellation because of no payment of annual fees	

Concepts



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Name	Image	Sections	Count	Query match
Corticotropin-Releasing Hormone Receptors		title,abstract,description	32	0.000
Corticotropin-Releasing Hormone Receptors		title,abstract,description	32	0.000
receptor antagonist		title,description	12	0.000
1H-pyrazolo[4,3-d]pyrimidine		title,description	4	0.000
compounds		claims,abstract,description	158	0.000
furanylmethyl		claims,abstract,description	45	0.000
alkyl group		claims,abstract,description	44	0.000
hydroxy group		claims,abstract,description	42	0.000
acid		claims,abstract,description	29	0.000
disease		claims,abstract,description	26	0.000
salts		claims,abstract,description	26	0.000
addition		claims,abstract,description	23	0.000
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⌘ nitro group	claims,description	6	0.000
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⌘ physiological condition	claims,description	4	0.000
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⌘ cyclopropyl group	claims,description	3	0.000
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⌘ imidazolyl group	abstract	1	0.000
⌘ pyrrolidinyl group	abstract	1	0.000
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Thiazolyl-pyrazolopyrimidine compounds as synthetic intermediates and related synthetic methods

Abstract

translated from Japanese

The present invention provides synthetic intermediates of the formula

and,
it relates to the use of synthetic intermediates in synthetic methods to produce compounds of the formula

Classifications

☞ C07D487/04 Ortho-condensed systems

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documents, Priority and Related Applications

External links: Espacenet, Global Dossier, Discuss

Claims (18)

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translated from: Japanese

Compounds of formula

Wherein R^1 and R^2 are independently ethyl or n-propyl, or a salt thereof. The compound according to claim 1, or a salt thereof, wherein R^1 and R^2 are each ethyl. A synthetic method for preparing a compound of the formula:

(Wherein R^1 and R^2 are independently ethyl or n-propyl)

(i) the following compound or a salt thereof:

2,4-dichlorothiazole or a salt thereof in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine, and a base selected from K_3PO_4 and Cs_2CO_3 . Reacting to form a compound of the formula:

(ii) reacting the product of step (i) with morpholine or a salt thereof in the presence of a suitable inorganic base. The method of claim 3, wherein R^1 and R^2 are each ethyl. The method according to claim 3 or 4, wherein the copper halide is CuCl. The method according to any one of claims 3 to 5, wherein the ligand is 1,10-phenanthroline. Base in step (i) A method as claimed in any one of claims 3 to 6. Base in Step (ii) A method according to any one of claims 3 to 7 is K_2CO_3 . R^1 and R^2 are each ethyl, copper halide is CuCl, the ligand is 1,10-phenanthroline, the base in step (i) is Cs_2CO_3 , step (ii) The method according to claim 3, wherein the base in (ii) is K_2CO_3 . The method according to claim 9, wherein the solvent in step (i) is 1,4-dioxane or 2-MeTHF / DMAC, and the solvent in step (ii) is morpholine, 2-MeTHF, or 2-propanol. A synthetic method for preparing a compound of the formula:

(Wherein R^1 and R^2 are independently ethyl or n-propyl)

(i) a compound of the following formula or a salt thereof:

Reacting with an excess of morpholine or a salt thereof in the presence of a suitable solvent. The method according to claim 11, wherein the solvent is 2-methyltetrahydrofuran.

The method according to claim 11, wherein the solvent is 2-propanol. The method according to any one of claims 11 to 13, wherein R^1 and R^2 are each ethyl. A synthetic method for preparing a compound of the formula:

(Wherein R^1 and R^2 are independently ethyl or n-propyl)

(i) a compound of the following formula or a salt thereof:

2,4-dichlorothiazole or a salt thereof in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine, and a base selected from K_3PO_4 and Cs_2CO_3 . Reacting to form a compound of the formula:

(ii) reacting the product of step (i) with an excess of morpholine or a salt thereof in the presence of a suitable solvent. The process according to claim 15, wherein the solvent is 2-

methyltetrahydrofuran. The method according to claim 15, wherein the solvent is 2-propanol. The method according to any one of claims 15 to 17, wherein R^1 and R^2 are each ethyl.

Description

translated from Japanese

The present invention relates to novel intermediates and methods in the synthesis of thiazolyl-pyrazolopyrimidine compounds where the final compounds are useful as CRF-1 receptor antagonists for the treatment of certain mental and neuroendocrine diseases.

Corticotropin releasing factor (CRF) is a peptidic hypothalamic hormone, which also has a wide range of physiological actions that harmonize with the role of neurotransmitters or neuromodulators in the brain. CRF has been implicated in a wide range of psychiatric and neuroendocrine disorders, including alcohol and drug abuse and associated withdrawal symptoms, as well as depression and anxiety. CRF-1 receptor antagonists have been particularly implicated in the treatment of alcoholism and depression.

Certain thiazolyl-pyrazolo [1,5-a] pyrimidines have been found to be particularly useful as CRF-1 antagonists. For example, 7- (1-ethyl-propyl) -3- (4-chloro-2-morpholin-4-yl-thiazol-5-yl) -2,5-dimethyl-pyrazolo described in Patent Document 1 [1,5-a] pyrimidine and 7- (1-propyl-butyl) -3- (4-chloro-2-morpholin-4-yl-thiazol-5-yl) -2,5-dimethyl-pyrazolo [1,5-a] pyrimidine. Non-Patent Document 1 discloses recent advances in copper-catalyzed arylation reactions with different substrates.

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J. et al. Am. Chem. Soc. 130, 1128-1129, 2008

The present invention provides novel synthetic intermediates and synthetic methods that use these intermediates to generate thiazolyl-pyrazolo [1,5-a] pyrimidine CRF-1 receptor antagonists in a more economical and higher yield. Furthermore, certain embodiments of the methods claimed herein avoid the use of mutagens and environmentally toxic catalysts compared to currently known synthetic methods (eg, those described in US Pat.

in a first embodiment of the invention, the following compound of formula I

Wherein R^1 and R^2 are independently ethyl or n-propyl.

in a first preferred embodiment, R^1 and R^2 are each ethyl. In a second preferred embodiment, R^1 and R^2 are each n-propyl.

in another aspect of the invention, a synthetic method for preparing the following compound of formula II comprising:

(Wherein R^1 and R^2 are independently ethyl or n-propyl)

(i) a compound of formula III below or a salt thereof:

2,4-di-chlorothiazole or a salt thereof in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine, and a base selected from K_2CO_3 and Ca_2CO_3 Reacting to form a compound of formula I above.

(ii) reacting a compound of formula I with morpholine or a salt thereof in the presence of a suitable inorganic base;

A method comprising:

in a first preferred embodiment of this aspect of the invention, R^1 and R^2 are each ethyl. In a second preferred embodiment of this aspect of the invention, R^1 and R^2 are each n-propyl.

Suitable copper halide catalysts include CuI, CuBr and CuCl, with CuCl being preferred.

The use of a copper ligand promotes an efficient catalytic reaction with copper ions. Both 1,10-phenanthroline and bipyridine are effective ligands in the present method, with 1,10-phenanthroline being preferred. If bipyridine is used, a high mole percent of bipyridine and copper is necessary to obtain a high yield. About 0.9 to about 1.1 equivalents (eg, about 1 equivalent) for bipyridine and about 0.5 to about 1.1 equivalents (eg, about 1 equivalent) for the copper source are required and CuCl is used. It is preferable.

When 1,10-phenanthroline is used, it can be used efficiently in a catalytic amount and in a catalytic amount of a copper source. For example, each is used at about 5 to 50 mole percent (0.05 to 0.50 equivalents) using the preferred copper source CuCl. In one embodiment, 1,10-phenanthroline and a copper catalyst (such as CuCl) are used at about 5-50 mole percent (0.05-0.50 equivalents). In another embodiment, 1,10-phenanthroline and a copper catalyst (such as CuCl) are used at about 10 $\pm$ 1 mole percent (0.10 equivalent). In yet another embodiment, 1,10-phenanthroline and a copper catalyst (such as CuCl) are used at about 50 $\pm$ 1 mole percent (0.50 equivalents).

The reaction of step (i) is base driven and sensitive to the selected base. Di-chlorothiazole reagents are bases and temperature labile, and when the selected base is too strong and / or the reaction temperature is too high (eg, using t-butoxy lithium or t-butoxy potassium and / or Or temperatures above about 120 ° C.) are susceptible to decomposition. In this case, suitable bases for step (i), a K_2CO_3 and Ca_2CO_3 is preferably used. Similarly, it is preferred to carry out the reaction of step (i) at a

temperature of about 80-120 ° C.

The reaction of step (i) involves the use of a suitable solvent that is an aprotic solvent (eg, 1,4-dioxane, 2-MeTHF, DMAC, CPME, propanenitrile, 2-MeTHF / DMAC, n-BuOAc and DMF). Less sensitive to the solvent selected. The ratio of the 2-MeTHF / DMAC co-solvent system is 70/30 to 80/20, preferably, for example, 80/20 2-MeTHF / DMAC.

The reaction of step (ii) is less sensitive to inorganic bases and selected solvents. Suitable CO_3 , Na_2CO_3 , K_2CO_3 , K_3PO_4 , such as NaOH and the like. K_2CO_3 and K_3PO_4 are preferred, and K_2CO_3 is particularly preferred.

Suitable solvents for the reaction of step (ii) mainly include polar solvents such as methanol, ethanol, n-propanol, 2-propanol, n-butanol, acetonitrile, 2-MeTHF, and morpholine. Morpholine is preferred in that it is an excellent solvent and a reactant in the reaction of step (ii).

The preferred reaction temperature for the reaction of step (ii) is about 60-120 ° C.

in one preferred embodiment of the invention, the synthesis method comprises:

(i) a compound of formula III below or a salt thereof.

(Wherein R^1 and R^2 are independently ethyl or n-propyl), CuCl, 1,10-phenanthroline, and in the presence of a base selected from K_2CO_3 and Ca_2CO_3 Reacting with 2,4-di-chlorothiazole or a salt thereof to form a compound of formula I above, and

(ii) reacting the compound of formula I with morpholine or a salt thereof in the presence of K_2CO_3 .

In this embodiment of the method, the reaction of step (i) comprises as solvent system about 5-50 mole percent (especially about 30 mole percent) CuCl and about 5-50 mole percent (especially about 30 mole percent). It is more preferable to carry out the reaction at about 80 to 120 ° C, using 1,10-phenanthroline (containing 2-MeTHF / DMAC (particularly including about 80/20 2-MeTHF / DMAC)). In the reaction of step (ii), it is more preferable to use morpholine as a solvent and K₂CO₃ as a base.

In another aspect of the invention, a synthetic method for preparing a compound of the formula:

Wherein R¹ and R² are independently ethyl or n-propyl.

(i) a compound of the following formula or a salt thereof:

Reacting with an excess of morpholine or a salt thereof in the presence of a suitable solvent;

A method comprising:

In one embodiment of this aspect of the invention, a synthetic method for preparing a compound of the formula:

(Wherein R¹ and R² are independently ethyl or n-propyl)

(i) a compound of the following formula or a salt thereof:

2,4-dichlorothiazole or a salt thereof in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine, and a base selected from K₂PO₄ and Cs₂CO₃. Reacting to form a compound of the formula: and

(ii) reacting the product of step (i) with an excess of morpholine or a salt thereof in a suitable solvent.

A method comprising:

In this aspect of the invention, various aprotic solvents may be suitable, but the preferred solvents are 2-MeTHF and 2-propanol. In a preferred embodiment, 2-propanol is used as the solvent. Surprisingly, it has been found that the use of 2-propanol reduces the reaction time by a factor of about 3 over the previously tested solvent system. More surprisingly, it has been found that the use of 2-propanol provides the desired amination product with high purity even in the presence of competing nucleophilic alcohols. Furthermore, the use of 2-propanol also simplifies the final product work-up. In other words, by directly crystallizing from this solvent, further solvent exchange before crystallization can be omitted.

In this aspect of the invention, it has also surprisingly been found that morpholine can function as a suitable base for the amination reaction, thus eliminating the need for additional bases to drive the reaction. In addition, the yield was improved while maintaining the quality of the final product. The reduction in the amount of morpholine used is also beneficial in the final work-up of the product. In one embodiment, 2-MeTHF is used as the solvent and the reaction is performed with between about 4.0 equivalents and about 6.0 equivalents (eg, 5.55 equivalents) morpholine or a salt thereof. In another embodiment, 2-propanol is used as the solvent and the reaction is performed with between about 3.0 equivalents and about 4.0 equivalents (eg, 3.3 equivalents) morpholine or a salt thereof.

Accordingly, in one embodiment of the present invention is a synthetic method for preparing a compound of the formula:

(i) a compound of the following formula or a salt thereof:

Reacting with 2,4-di-chlorothiazole or a salt thereof in the presence of copper chloride, 1,10-phenanthroline and Cs₂CO₃ to form a compound of the formula:

(ii) reacting the product of step (i) with an excess of morpholine or a salt thereof in a solvent of 2-propanol;

A method comprising:

Abbreviations used in the present specification are as follows.

CPME means cyclopentyl methyl ether

DMAC means N, N-dimethylacetamide.

DMF means dimethylformamide.

EtOAc means ethyl acetate.

2-MeTHF means 2-methyltetrahydrofuran.

The 2-MeTHF / DMAC system means 2-methyltetrahydrofuran and N, N-dimethylacetamide in a cosolvent system in a ratio of about 70/30 and about 80/20.

n-BuOAc means n-butyl acetate.

XRPD means X-ray powder diffraction.

DSC means differential scanning calorimetry.

Further preferred embodiments of the synthesis method of the invention are described in the following examples.

Example 1. 7-(1-Ethyl-propyl)-3-((2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

7-(1-Ethyl-propyl)-3-Iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (1.93 g, 3.00 mmol), K₂PO₄ (1.95 g, 9.00 mmol), 2,4-dichlorothiazole (0.58 g, 3.75 mmol), 1,10-phenanthroline (0.05 g, 0.30 mmol) and anhydrous DMAC (5 mL) were added to a magnetic stir bar, thermocouple and N₂ injection. Place in a round bottom flask with an inlet. The yellow heterogeneous reaction mixture was degassed with N₂ (gas) for 30 min, then CuI (0.06 g, 0.30 mmol) was added in one portion, followed by degassing with N₂ (gas) for another 30 min. To do. The reaction mixture is stirred at 120 ° C, for about 6 hours. Cool the reaction mixture to room temperature overnight, add toluene (10 mL) and stir for 1 hour. Purify the mixture on silica gel eluting with toluene (10 mL). Extract with 1M HCl (10 mL), water (10 mL), brine (10 mL) and concentrate under reduced pressure to give a yellow solid. Recrystallize the solid from methanol (5 mL) to give the title compound as a yellow crystalline solid. (0.78 g, 70% yield, > 99% purity by LC) MS (ES) = 369 (M + 1). ¹H NMR (CDCl₃) = 6.5 (1H, s); 3.6 (1H, m); 2.6 (3H, s); 2.5 (3H, s); 1.9 (4H, m); 0.9 (6H, t).

Example 2. 7-(1-Ethyl-propyl)-3-((4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

7-(1-Ethyl-propyl)-3-Iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (0.57 g, 1.00 mmol), K₂CO₃ (0.28 g, 2.00 mmol) and anhydrous morpholine (5 mL) are placed in a round bottom flask equipped with a magnetic stir bar and N₂ inlet. The yellow mixture is stirred at 100 ° C, for about 4 hours, during which time the reaction becomes homogeneous. The reaction mixture is cooled to room temperature, H₂O (10 mL) is added and the heterogeneous reaction mixture is stirred at room temperature overnight. Collect the yellow solid by filtration, wash with H₂O and air dry overnight to give the crude title compound (391 mg). Recrystallize from isopropyl alcohol (3 mL) to give the title compound as a pale yellow crystalline solid (380 mg, 90.5% yield, > 99% by LC). MS (ES) = 420 (M + 1). ¹H NMR (CDCl₃) = 6.45 (1H, s), 3.81 (m, 4H); 3.62 (1H, m); 3.50 (m, 4H); 2.6 (3H, s); 2.45 (3H, s); 1.65 (4H, m); 0.9 (6H, t).

Example 3

The reaction of Example 1 is carried out with various other catalysts, ligands, bases and solvents, which are 7-(1-ethyl-propyl)-3-((2,4-dichloro-thiazol-5-yl)-. It has been found that it has the following effects on the production of 2,5-dimethyl-pyrazolo[1,5-a]pyrimidine. (See Tables 1-4).

(The reaction was performed with 1.2 mmol of 2,4-dichlorothiazole, 1 mmol of 7-(1-ethyl-propyl)-3-Iodo-2,5-dimethyl-pyrazolo[1,5-a] in 4 mL of DMAC. Run in a parallel reaction vessel with pyrimidine, 0.5 mmol CuI, 0.5 mmol ligand and 2.1 mmol Cs₂CO₃. The reaction was degassed under N₂ for 30 min and then at 80-100 ° C. In

between and heat overnight under N₂. The percentage of product is measured as a percentage of the total area under the HPLC curve for the product peak, longer reaction times are shown in parentheses.)

(The reaction was performed with 1.2 mmol of 2,4-dichlorothiazole, 1 mmol of 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine in parallel reaction vessel with pyrimidine, 0.25 mmol CuI, 0.25 mmol 1,10-phenanthroline and 2.1 mmol Cs₂CO₃. The reaction is degassed under N₂ for 30 min, it is then heated overnight under N₂ at 100 ° C. The percentage of product is measured as a percentage of the total area under the HPLC curve for the product peak.

(The reaction was performed with 1 mmol of 2,4-dichlorothiazole, 1 mmol of 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine in 3 mL of DMAc, The reaction is carried out in parallel reaction vessels with 0.05 mmol CuX, 0.01 mmol 1,10-phenanthroline and 3 eq K₂PO₄. The reaction is degassed under N₂ for 30 min and then at 100 ° C. Heat overnight under N₂. The percentage of product is measured as a percentage of the total area under the HPLC curve for the product peak.)

(The reaction was performed with 1 mmol 2,4-dichlorothiazole, 1 mmol 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine, 0.1 mmol CuI. Run in a parallel reaction vessel with 0.1 mmol of 1,10-phenanthroline and 2.1 mmol of base and degas for 30 minutes before adding 3 mL of DMAc. The reaction is degassed for 10 minutes under N₂. And then heated overnight under N₂ at 100 ° C. The percentage of product is measured as a percentage of the total area under the HPLC curve for the product peak.)

Example 4 Use of morpholine as both reactant and base in 2-MeTHF as solvent

7-(1-Ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (15.2 g, 41.16 mmol) is added to a 250 mL 3-neck round bottom flask followed by addition of 2-MeTHF (61 mL, 4.0 vol) and the tan slurry is stirred at about 20 ° C. for 5 minutes. Morpholine (19 g, 218.18 mmol) is then added over 2-5 minutes. The contents are heated to reflux and maintained at reflux for 12 hours. The slurry is cooled to 25 ° C. followed by the addition of 2-MeTHF (58 mL, 3.5 vol) and water (38 mL, 2.5 vol). The reaction mixture is heated to 40 ° C. in doing so, a homogeneous solution with two different layers is formed. Separate the layers and filter the organic layer and concentrate to about 3 volumes at atmospheric pressure. Add 4 volumes of 2-propanol (61 mL). Concentrate the solution to about 3 volumes, then add 4 volumes of 2-propanol (61 mL), reconcentrate to about 3 volumes, then add another 5 volumes of 2-propanol (91 mL) and reflux for 15 minutes. The clear solution was cooled slowly to 75 ° C. and stirred in 2 mL of 2-propanol 0.45 g of 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine seed crystals, rinse with 2 mL of 2-propanol and transfer to crystallization flask. Cool the slurry to between 0-5 ° C. maintain for 1 hour, filter, and rinse the product with 2-propanol (30 mL, 2 vol). The solid was dried in a vacuum oven at 60 ° C. to give 16.92 g of 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine is obtained. The purity of the product by HPLC assay is 100.00%. The product XRPD and DSC data are consistent with the reference sample. MS (ES) = 420 (M + 1).

Example 5 Use of morpholine as both reactant and base in 2-propanol as solvent 7-(1-Ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (11.64 mmol) is placed in a 100 mL 3-neck round bottom flask followed by 2-propanol (16 mL, 3.72 volumes). Stir the tan slurry at about 20 ° C. for 5 minutes. Then morpholine (3.3 g, 37.84 mmol) is added over 2-5 minutes. Reflux the contents for 6 hours. Cool the slurry to 25 ° C. 2-Propanol (32 mL, 7.44 vol) and water (8.6 mL, 2.0 vol) are added and the mixture is heated to 70-75 ° C., filtered and concentrated to about 5 vol at atmospheric pressure. The clear solution was gradually cooled to 55 ° C. and stirred in 0.5 mL of 2-propanol, 0.06 g of crystalline 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholine). Add seed crystals of 4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine, rinse with an additional 0.5 mL of 2-propanol and add to the crystallization flask. Cool the slurry to 0-5 ° C. maintain for 1 hour, filter, and rinse the product with 2-propanol (9 mL, 2.1 vol). 4.6 g of dry 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2 by suction drying under vacuum at 60 ° C., 5-dimethyl-pyrazolo [1,5-a] pyrimidine (88.8% yield, purity by HPLC assay is 99.88%). MS (ES) = 420 (M + 1).

Example 6 7-(1-Ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine 7-(1-ethyl)-Propyl)-3-iodo-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (10 g, 29.17 mmol), 2,4-dichlorothiazole (5.2 g, 33.76 mmol), cesium carbonate (19.9 g, 61.67 mmol) and 1,10-phenanthroline (1 g, 5.5 mmol) are placed in a 250 mL 3-neck round bottom flask followed by 2-MeTHF (36 mL, 3.6 vol). The reaction mixture is degassed with nitrogen and then evacuated. Cuprous chloride (0.57 g, 5.7 mmol), DMAc (10 mL, 1 vol) and 2-MeTHF (4 mL, 0.4 vol) are added sequentially. The reaction mixture is degassed with nitrogen and then evacuated. The contents are refluxed for 20 hours. The reaction mixture is cooled to about 70 ° C. and 2-MeTHF (100 mL, 10 vol) is added. The contents are filtered at about 70 ° C and the residual cake is washed with 2-MeTHF (80 mL, 8 vol) at about 65-72 ° C. Transfer the filtrate to a separatory funnel and extract with water. The organic layer is separated and washed with dilute HCl. The resulting organic layer is treated with Darco G60, heated (60 ° C.) and filtered. Concentrate the filtrate to atmospheric pressure to about 2.8 volumes. Add 23 mL of 2-propanol followed by reconcentration to about 2.8 volumes. Add another 25 mL of 2-propanol followed by reconcentration to about 2.8 volumes. Finally, 48 mL of 2-propanol is added. Cool the contents to -7 ° C., maintain at -7 ° C. for 1 hour, filter, and rinse with 20 mL of cooled 2-propanol. The product is sucked dry and then vacuum dried at 60 ° C. to give 9.41 g of 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (product purity by HPLC assay is 95.88%). MS (ES) = 369 (M + 1).

Example 7 7-(1-Ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine using a 1,4-dioxane solvent and a CuCl catalyst Synthesis of 5-a] pyrimidine

Dioxane (19.66g, 0.2093), 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo [1,5-a] pyrimidine (1.0 equiv) is added 2,4-dichloro-thiazole (0.54 eq) to the reaction vessel under N₂. The reaction solution was purged with N₂ three times, degassed with N₂ for 0.5-1 h, then 1,10-phenanthroline (0.3 eq) and CuCl (0.3 eq) were added under N₂. In addition, degas with N₂ for 0.5-1 hr. Heat the reaction vessel to 100-110 ° C. under N₂. The mixture is stirred at 100-110 ° C. for 22-24 hours. Cool to 10-20 ° C., add water (10 V) and CH₃OH (5 V) and stir the mixture at 10-20 ° C. for 1-1.5 hours. The suspension is filtered, the wet cake in water is resuspended, stirred at 10-20 ° C. for 1-1.5 hours, and the suspension is filtered again. The wet cake Add to H₂ under n-heptane (16V) and EtOAc (2V). The reaction vessel is heated to 40 ° C. to 50 ° C. under N₂.

Activated carbon (0.1X) is added at 40-50 ° C. The reaction vessel is heated to 55-65 ° C. under N₂ and stirred at 55-65 ° C. for 1-1.5 hours. The suspension is filtered through diatomaceous earth (0.4X) at 40-55 ° C. The cake is washed with n-heptane (2.5V). Transfer the filtrate to another reaction vessel. EtOAc (15V) is added and the organic layer is washed 3 times with 2N HCl (10V) followed by 2 times with water (10X, 10V). The organic layer is concentrated to 3-4V below 50 ° C. The mixture is heated to 80-90 ° C. The mixture is maintained at this temperature for 40-60 minutes. The mixture is cooled to 0-5 ° C, stirred at 0-5 ° C for 1-1.5 hours and filtered. The cake is washed with n-heptane (1 V) and vacuum dried at 45-50 ° C. for 8-10 hours. The crude product is dissolved in 2-propanol (7.5 V) under N₂ and recrystallized from 2-propanol. The cake is dried in a vacuum oven at 45-50 ° C. for 10-12 hours (55-80% yield). ¹H NMR δ 6.537 (s, 1H) 3.591-3.659 (m, 1H, J = 6.8 Hz), 2.593 (s, 3H), 2.512 (s, 3H), 1.793-1.921 (m, 4H), 0.885-0.903 (m, 6H).

Patent Citations (3)

Publication number	Priority date	Publication date	Assignee	Title
Family To Family Citations				

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MY146388A	2006-09-20	2012-08-15	Lilly Co Eli	Thiazole pyrazolopyrimidines as crrl receptor antagonists
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Publication number	Priority date	Publication date	Assignee	Title
JP2020530832A *	2017-08-14	2020-10-29	スブルース バイオサイエンスズ インコーポレイテッド	Corticotropin-releasing factor receptor antagonist

Family To Family Citations

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Priority And Related Applications

Applications Claiming Priority (3)

Application	Filing date	Title
US10215308P	2008-10-02	
US61/102,153	2008-10-02	
PC1/US2009/058722	2009-09-29	Thiazolyl-pyrazolopyrimidine compounds as synthetic intermediates and related synthetic processes

Legal Events

Date	Code	Title	Description
2012-09-28	A621	Written request for application examination	Free format text: JAPANESE INTERMEDIATE CODE: A621 Effective date: 20120927
2014-03-17	TRDD	Decision of grant or rejection written	
2014-03-26	A01	Written decision to grant a patent or to grant a registration (utility model)	Free format text: JAPANESE INTERMEDIATE CODE: A01 Effective date: 20140325
2014-04-17	A61	First payment of annual fees (during grant procedure)	Free format text: JAPANESE INTERMEDIATE CODE: A61 Effective date: 20140409
2014-04-18	R150	Certificate of patent or registration of utility model	Ref document number: 5524221 Country of ref document: JP Free format text: JAPANESE INTERMEDIATE CODE: R150
2017-04-11	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2018-04-17	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2019-04-16	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2020-04-08	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
2021-04-14	R250	Receipt of annual fees	Free format text: JAPANESE INTERMEDIATE CODE: R250
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Concepts

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compounds		claims,abstract,description	31	0.000
iso-propanol		claims,description	60	0.000
solvent		claims,description	29	0.000
salts		claims,description	26	0.000
sodium chloride		claims,description	26	0.000
morpholine		claims,description	21	0.000
morpholine		claims,description	21	0.000
[1,10]phenanthroline		claims,description	20	0.000

⌘ ethyl group	claims,description	16	0.000
⌘ copper	claims,description	15	0.000
⌘ copper	claims,description	15	0.000
⌘ copper halide	claims,description	15	0.000
⌘ 2,4-dichloro-1,3-thiazole	claims,description	14	0.000
⌘ Copper(I) chloride	claims,description	14	0.000
⌘ catalyst	claims,description	11	0.000
⌘ n-propyl group	claims,description	11	0.000
⌘ binding	claims,description	10	0.000
⌘ ligand	claims,description	10	0.000
⌘ 2,2'-bipyridyl	claims,description	8	0.000
⌘ 2-Methyltetrahydrofuran	claims,description	4	0.000
⌘ 1,4-dioxane	claims,description	3	0.000
⌘ inorganic bases	claims,description	3	0.000
⌘ method	claims	1	0.000
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(54) Title: METHODS OF TREATING CONGENITAL ADRENAL HYPERPLASIA

(57) Abstract: Patients with congenital adrenal hyperplasia (CAH) need ade-
quate 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.

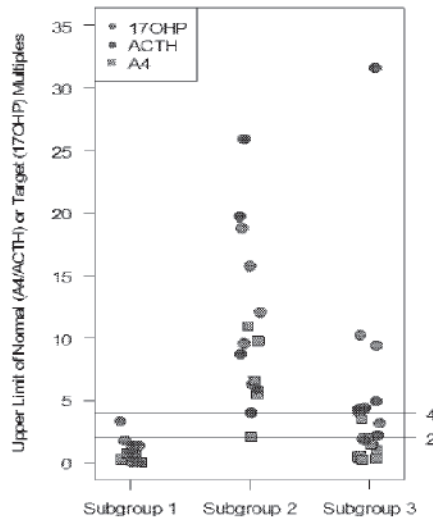


FIG. 1

[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))*

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- *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 (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 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 CRF₁ 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 adrenocorticotrophic hormone (ACTH), androstenedione (A4), 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone,

aldosterone, pregnenolone, 17 α -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 adrenocorticotrophic hormone (ACTH), androstenedione (A4), 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17 α -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.

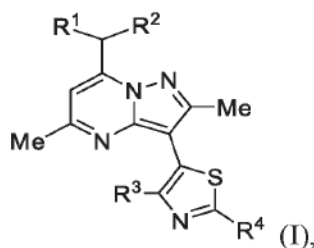
[0013] In some embodiments, the level of ACTH or A4 is 2 times, 1.5 times, 1.25 times, or 1 times said upper limit of said normal range of ACTH or A4 level of said subject. In some embodiments, the amount of said steroid or a pharmaceutically acceptable salt thereof comprises a range of about 10 mg to 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 CRF₁ antagonist or a pharmaceutically acceptable salt thereof comprises a range of about 10 mg to about 200 mg, wherein said CRF₁ 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 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.

[0017] In some embodiments, the CRF₁ antagonist is a compound of Formula (I):

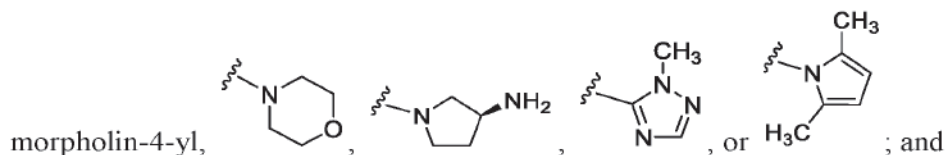


or a pharmaceutically acceptable salt thereof, wherein:

R¹ and R² are independently ethyl or *n*-propyl;

R³ is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R⁴ is hydrogen, Br, R^aR^bN-, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl,

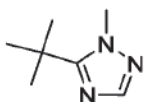


R^a and R^b are independently hydrogen, C₁-C₃alkyl, H₂NCH₂CH₂-, (CH₃)₃COC(O)NHCH₂CH₂-, or CH₃CH₂CH₂NHCH₂CH₂-.

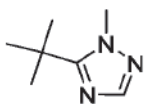
[0018] In some embodiments, R³ is Cl, Br, methyl, or trifluoromethyl.

[0019] The method of claims 38 or 39, wherein R³ is Cl, Br, or methyl.

[0020] In some embodiments, R⁴ is Br, R^aR^bN-, pyridin-4-yl, morpholin-4-yl, or

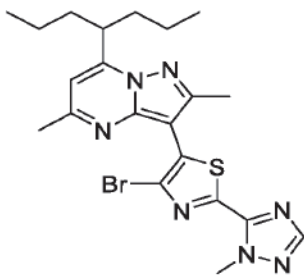


[0021] In some embodiments, R⁴ is morpholin-4-yl or



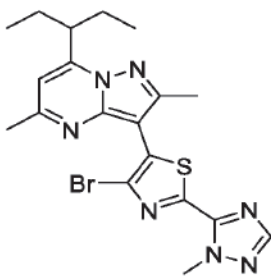
[0022] In some embodiments, R⁴ is hydrogen, Br, R^aR^bN- and R^a and R^b are independently C₁-C₃alkyl.

[0023] In some embodiments the compound is



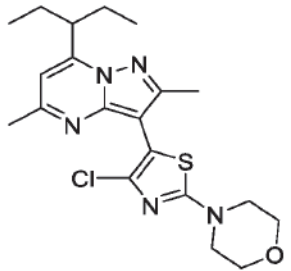
, or a pharmaceutically acceptable salt thereof.

[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 (CRF₁) antagonist or a pharmaceutically acceptable salt thereof, wherein said 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. 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 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 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- β hydroxylase deficiency, 17 α -hydroxylase deficiency, 3- β -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 adrenocorticotrophic 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.

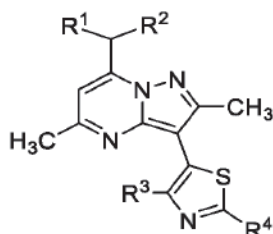
Compounds

[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]

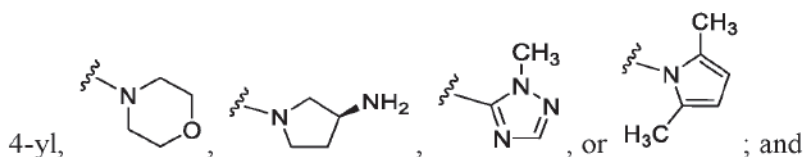
[0075] Formula (I)

[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;

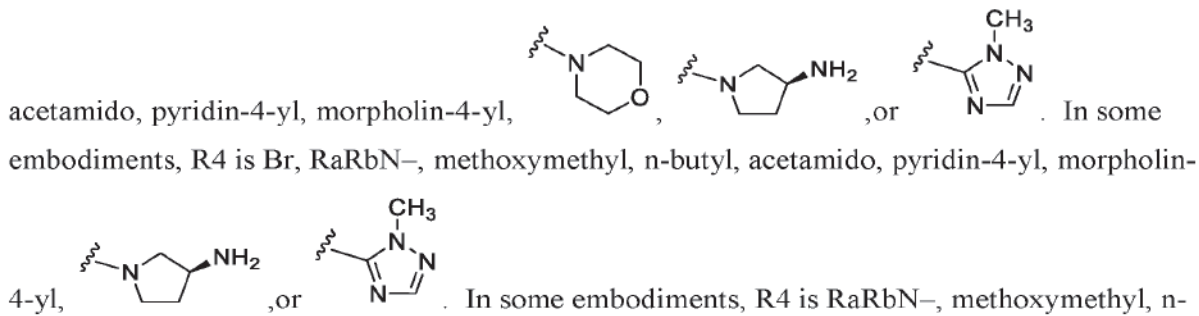
[0079] R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-

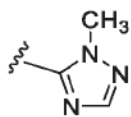


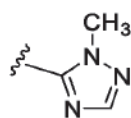
[0080] Ra and Rb are independently hydrogen, C1-C3 alkyl, H2NCH2CH2-, (CH3)3COC(O)NHCH2CH2-, or CH3CH2CH2NHCH2CH2.

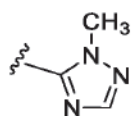
[0081] In some embodiments, R3 is hydrogen, Cl, Br, methyl, or trifluoromethyl. In some embodiments, R3 is hydrogen, Cl, Br, or methyl. In some embodiments, R3 is hydrogen, Cl, or Br. In some embodiments, R3 is hydrogen. In some embodiments, R3 is Cl. In some embodiments, R3 is Br.

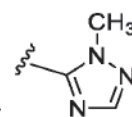
[0082] In some embodiments, R4 is hydrogen, Br, RaRbN-, methoxymethyl, n-butyl,



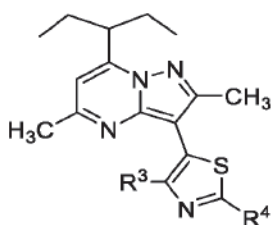
butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or . In some embodiments, R4 is

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):

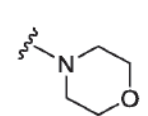
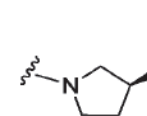
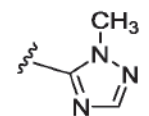
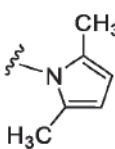


[0084] Formula (II)

[0085] or a pharmaceutically acceptable salt thereof, wherein

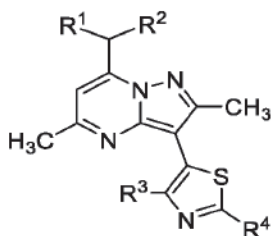
[0086] R3 is H, Cl, Br, methyl, trifluoromethyl or methoxy;

[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):



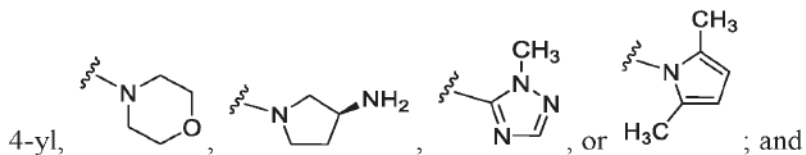
[0090] Formula (III)

[0091] or a pharmaceutically acceptable salt thereof, wherein

[0092] R1 and R2 are n-propyl;

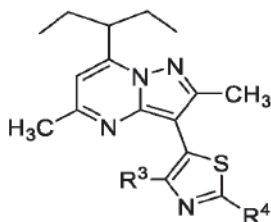
[0093] R3 is H, Cl, Br, methyl, trifluoromethyl or methoxy;

[0094] R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-



[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):

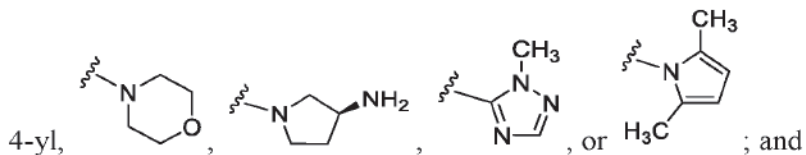


[0097] Formula IV

[0098] or a pharmaceutically acceptable salt thereof, wherein

[0099] R3 is Cl, Br, methyl, trifluoromethyl or methoxy;

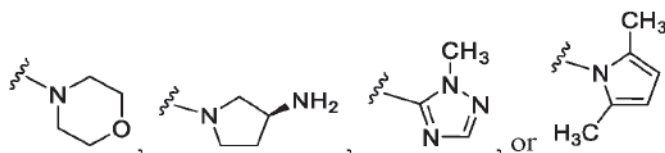
[0100] R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-



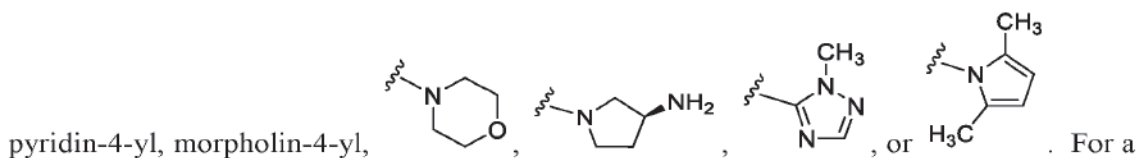
[0101] Ra and Rb are independently hydrogen, C1-C3 alkyl, H2NCH2CH2-, (CH3)3COC(O)NHCH2CH2-, or CH3CH2CH2NHCH2CH2.

[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.

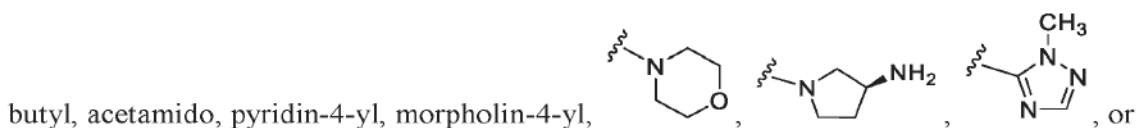
[0103] For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R₄ is Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



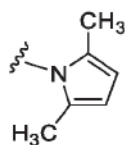
For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R₄ is Br, methoxymethyl, n-butyl, acetamido,



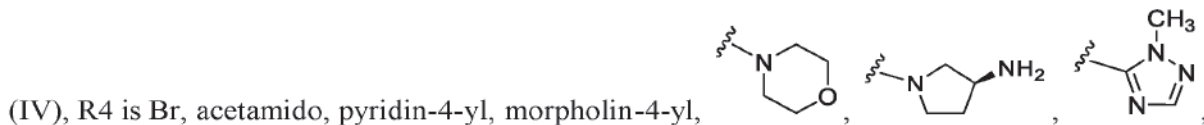
pyridin-4-yl, morpholin-4-yl, For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R₄ is Br, n-



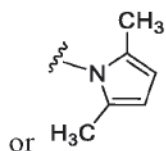
butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



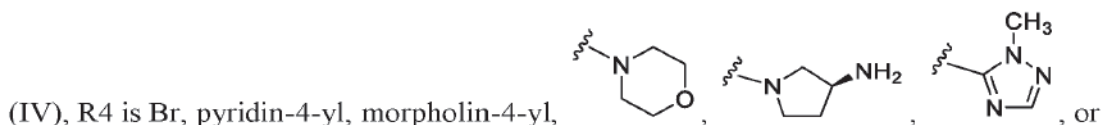
For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and



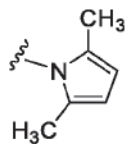
(IV), R₄ is Br, acetamido, pyridin-4-yl, morpholin-4-yl,



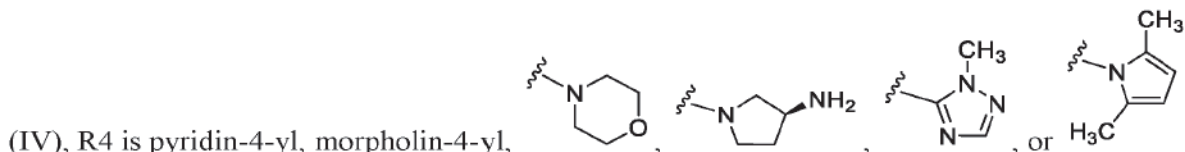
or For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and



(IV), R₄ is Br, pyridin-4-yl, morpholin-4-yl,

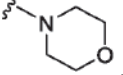
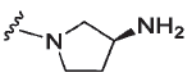
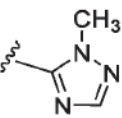
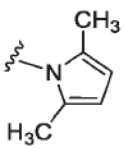


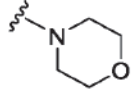
For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and

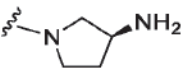
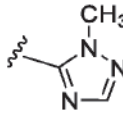
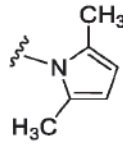


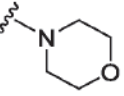
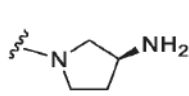
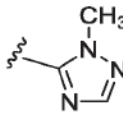
(IV), R₄ is pyridin-4-yl, morpholin-4-yl,

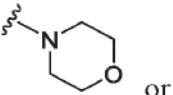
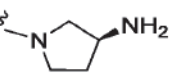
For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R₄ is

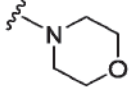
morpholin-4-yl, , , , or . For a compound or

pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is ,

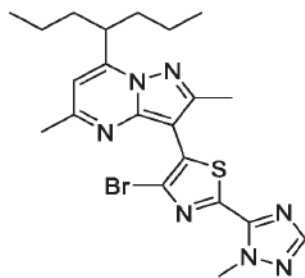
, , or . For a compound or pharmaceutically acceptable salt

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

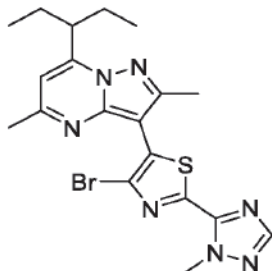
(I), (II), (III), and (IV), R4 is .

[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:



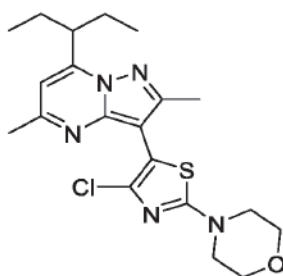
Compound 1

[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 CRF₁ 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.