SN003, CRA0450, SSR125543A, CP-316,311, CP-376,395, NBI-27914, ONO-2333Ms, NBI-34101, PF-572778, GSK561579 and GSK586529.

15. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is DMP-696.

16. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is CP-316,311.

17. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is SSR125543A.

18. CRHR1 antagonist for use according to any of the preceding claims, wherein CRH overactivity is detected by determining the status of one or more markers indicative for CRH overactivity.

19. CRHR1 antagonist for use according to claim 18, wherein the marker is selected from the group consisting of a biomarker, a set of biomarkers and a clinical marker.

20. CRHR1 antagonist for use according to any of claim 19, wherein the biomarker or the set of biomarkers is obtained by a genome-wide screening for single nucleotide polymorphisms in patients with depressive and/or anxiety symptoms.

21. CRHR1 antagonist for use according to claims 19 or 20, wherein the biomarker or the set of biomarkers is selected from the group comprising:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,

- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,
- SNP rs11025990,
- SNP rs3758562, and/or
- SNP rs10156056.

22. CRHR1 antagonist for use according to any of claims 19 to 21, wherein the biomarker or the set of biomarkers constituting a marker for CRH activity is selected from one or more biomarkers from the group comprising:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,

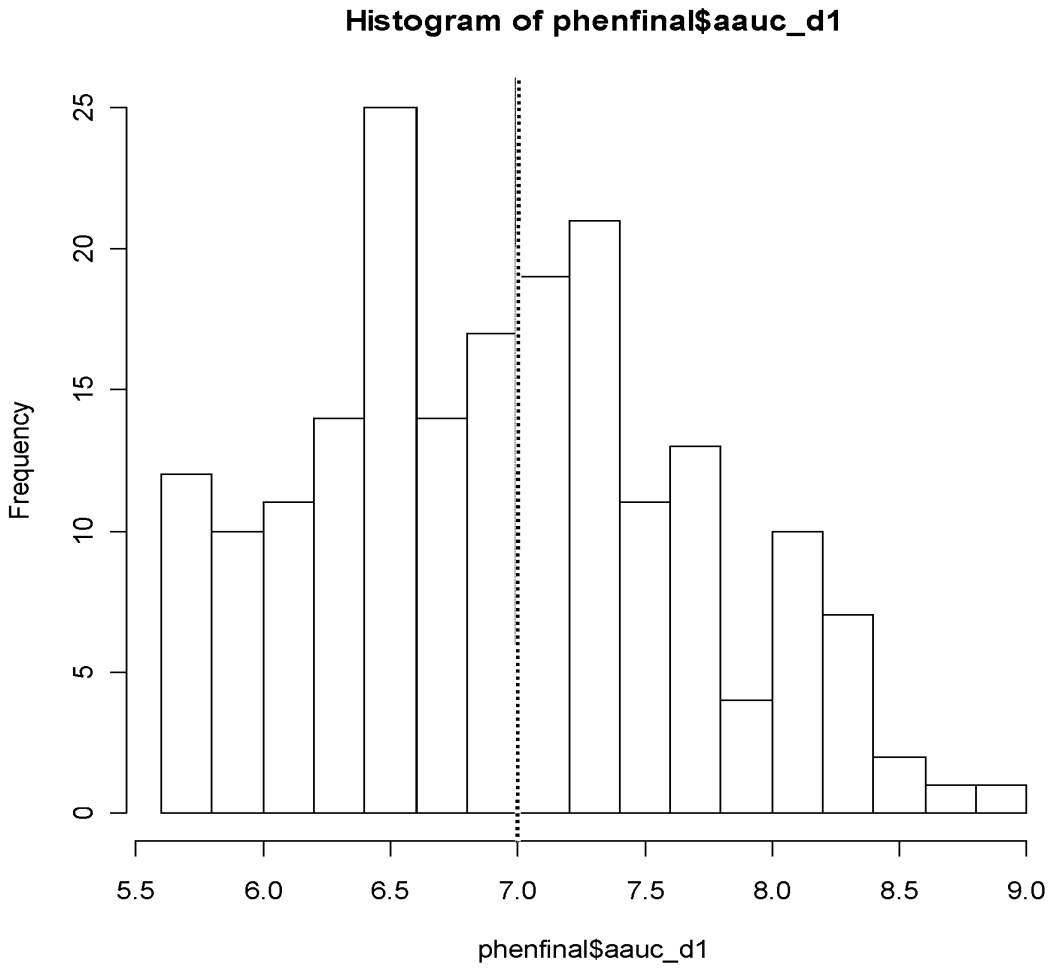
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G, and/or
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

23. CRHR1 antagonist for use according to any of claims 19 to 22, wherein the set of biomarkers comprises at least 15, at least 20 or at least 25 of the biomarkers as defined in claims 21 or 22.

24. CRHR1 antagonist for use according to any of claims 19 to 23, wherein the set of biomarkers consists of the biomarkers as defined in claims 21 or 22.

25. CRHR1 antagonist for use according to any of claims 18 or 24, wherein the biomarker is REM density.

26. CRHR1 antagonist for use according to any of claims 18 or 25, wherein the marker is a combination of a biomarker or set of biomarkers as defined in any of claims 20 to 24 with the biomarker REM density.


Histogram of phenfinal$aauc_d1
Frequency
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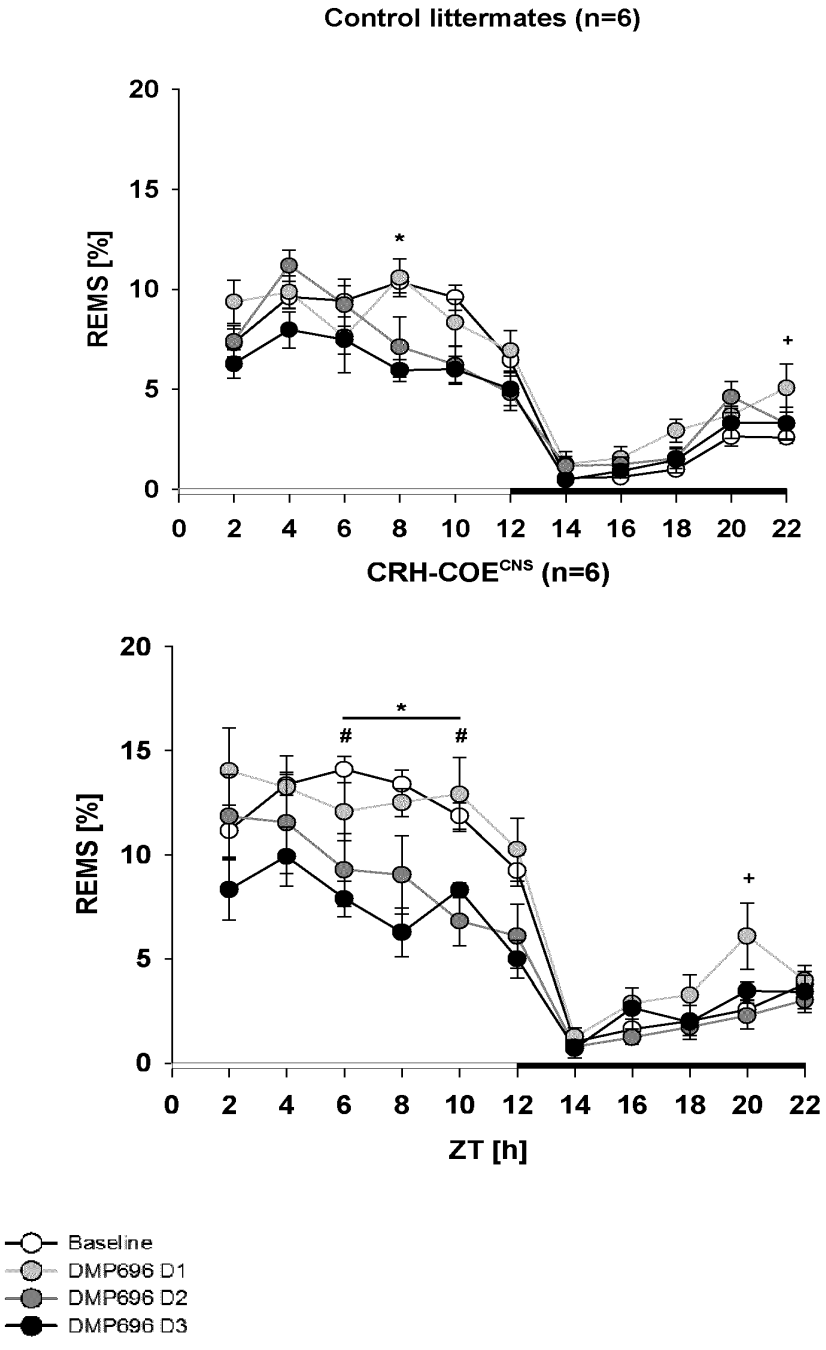
5
10
15
20
25
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
phenfinal$aauc_d1

Fig. 1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REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22
*
+
CRH-COE^CNS (n=6)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22
*
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#
+
ZT [h]
Baseline
DMP696 D1
DMP696 D2
DMP696 D3

Fig. 2

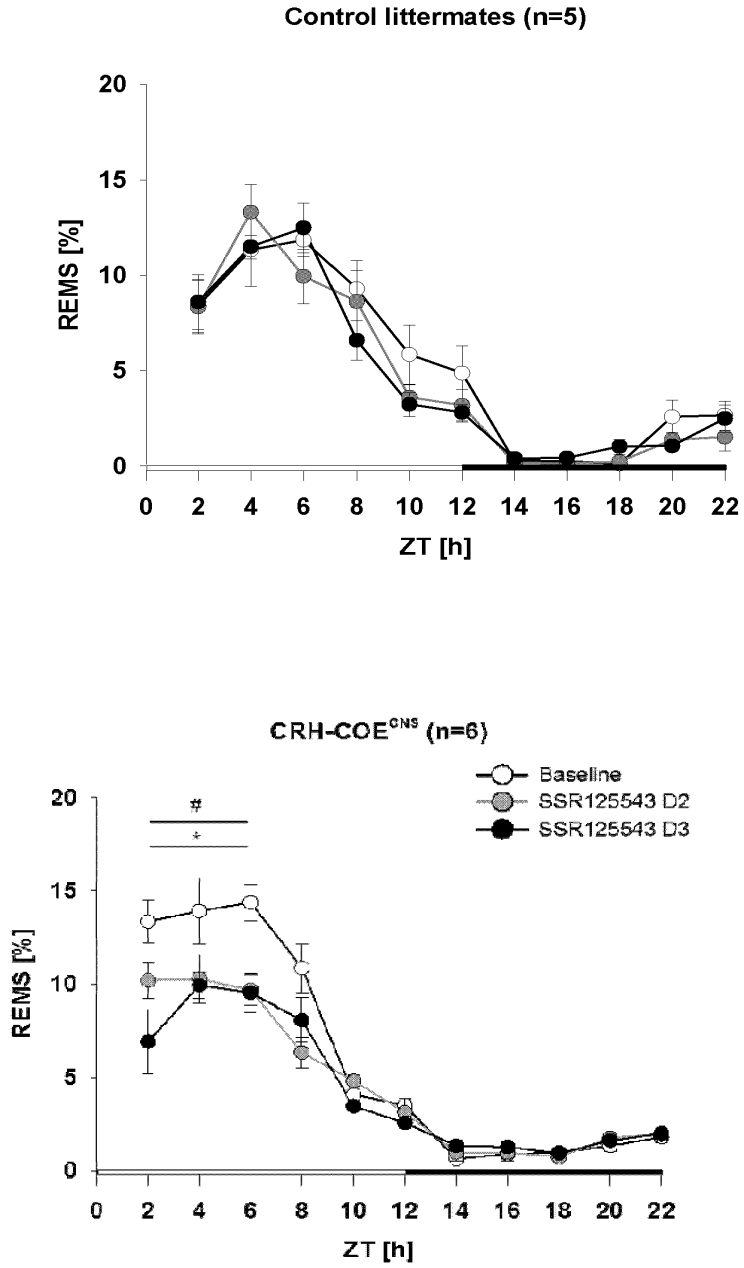
Control littermates (n=5)
REMS [%]
ZT [h]
CRH-COE^CNS (n=6)
Baseline
SSR125543 D2
SSR125543 D3
#
*

Fig. 3

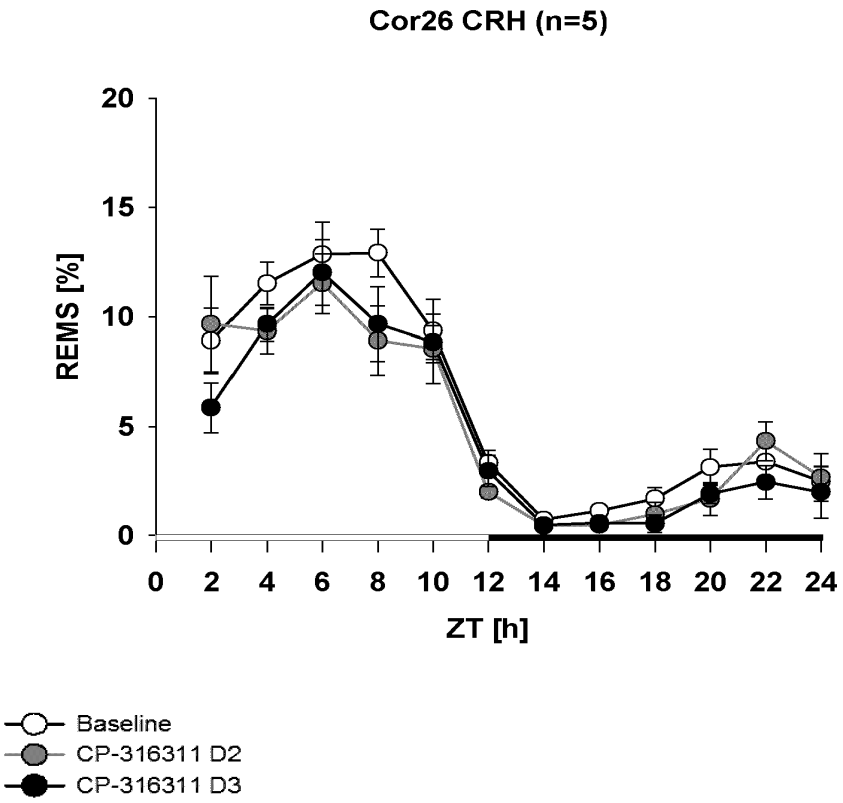
Cor26 CRH (n=5)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22 24
ZT [h]
Baseline
CP-316311 D2
CP-316311 D3

Fig. 4

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(71) Applicant: **SPRUCE BIOSCIENCES, INC.** [US/US]; 611 Gateway Boulevard, Suite 740, South San Francisco, California 94080 (US).

(72) Inventors: **REDDY, Dasharatha**; 611 Gateway Boulevard, Suite 740, South San Francisco, California 94080 (US). **RAJAGOPAL, Ashokraj**; 611 Gateway Boulevard, Suite 740, South San Francisco, California 94080 (US). **WANG, Lu**; 611 Gateway Boulevard, Suite 740, South San Francisco, California 94080 (US). **BARNES, Christopher**; 611 Gateway Boulevard, Suite 740, South San Francisco, California 94080 (US).

(74) Agent: **OLSHEMSKI, Stephen**; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, California 94304 (US).

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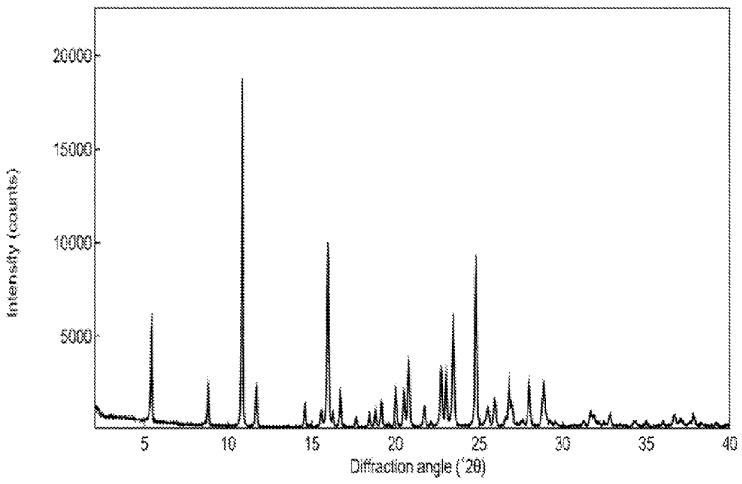
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,

(54) Title: CRYSTALLINE COMPOSITION OF TILDACERFONT AND METHODS OF USE AND PREPARATION THEREOF

FIG. 1



(57) Abstract: Described herein are crystalline composition, methods of making such crystalline composition, pharmaceutical compositions and medicaments comprising such crystalline composition, and methods of using such crystalline composition in the treatment of conditions, diseases, or disorders that would benefit from modulation of Corticotropin-releasing hormone receptor 1 (CRF1).

[Continued on next page]

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LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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CRYSTALLINE COMPOSITION OF TILDACERFONT AND METHODS OF USE AND PREPARATION THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/281,462 filed November 19, 2021 and U.S. Provisional Application No. 63/340,874 filed May 11, 2022, each of which is incorporated herein by reference in its entirety.

INCORPORATION BY REFERENCE

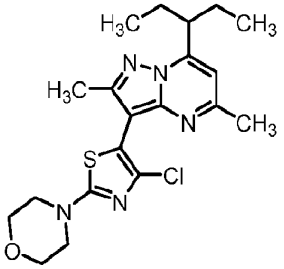
[0002] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BACKGROUND

[0003] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

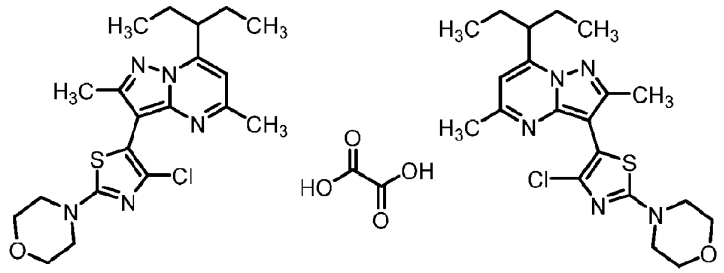
SUMMARY

[0004] In a first aspect, the present disclosure provides a crystalline composition comprising Compound I:



Compound I.

[0005] In some embodiments, the crystalline composition comprising Compound 1 comprises a crystalline composition comprising Formula I:



Formula I.

[0006] In some embodiments, the crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I) have unit cell parameters at T = 150°K of: a = 34.003(4) Å, b = 6.5843(13) Å, c = 21.062(5) Å; β = 108.703(12)°, V = 4466.5(15) $Å^3$ and a monoclinic C2/c space group.

[0007] In some embodiments, the crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I) is characterized by:

(a) an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å;

(b) an X-ray powder diffraction pattern substantially the same as shown in FIG. 1;

(c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C;

(d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C;

(e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2;

(f) a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C;

(g) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3; or

(h) combinations thereof.

[0008] In some embodiments, the crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I) is characterized by (a), (c), (d), and (f).

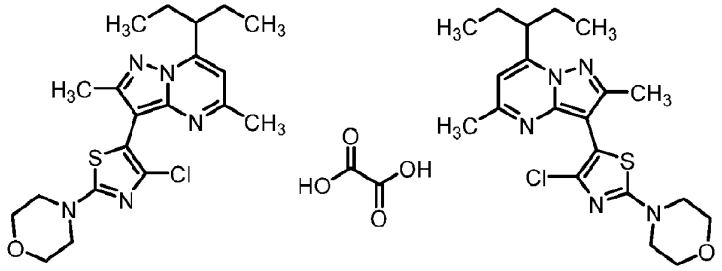
[0009] In some embodiments, the composition comprising a CRF1 antagonist (e.g., a crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by an X-ray powder diffraction pattern comprising one or more peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the CRF1 antagonist (e.g., crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from 5.44 ± 0.2° 2-θ, 20.78 ± 0.2° 2-θ, 22.74 ± 0.2° 2-θ, 23.04 ± 0.2° 2-θ, 26.80 ± 0.2° 2-θ, and 28.86 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least five peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the crystalline composition is characterized by an X-ray powder diffraction pattern substantially the same as shown in FIG. 1.

[0010] In some embodiments, the crystalline composition comprising a CRF1 antagonist (e.g., crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C. In some embodiments, the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset from about 160 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset from about 150 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset from about 160 °C to about 180 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising an endotherm with an onset at about 160 °C. In some embodiments, the crystalline composition is characterized by a DSC thermogram comprising a peak of about 166 °C. In some embodiments, the crystalline composition is

characterized by a DSC thermogram comprising a peak from about 166 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 166 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 160 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 150 °C to about 170 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 160 °C to about 180 °C. In some embodiments, the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2.

[0011] In some embodiments, the crystalline composition comprising a CRF1 antagonist (e.g., crystalline composition comprising Compound I (e.g., comprising Formula I)) is characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3. In some embodiments, the crystalline composition is characterized by a TGA thermogram comprising a loss in mass of more than 10% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a TGA thermogram comprising a loss in mass of less than about 15% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a TGA thermogram comprising a loss in mass of less than about 20% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition is characterized by a dynamic vapor sorption (DVS) trace substantially the same as shown in FIG. 4.

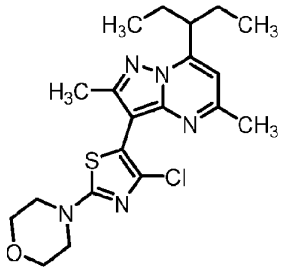
[0012] In some aspects, the present disclosure provides a pharmaceutical composition comprising crystalline composition comprising Formula I:



Formula I,

and at least one pharmaceutically acceptable carrier or excipient.

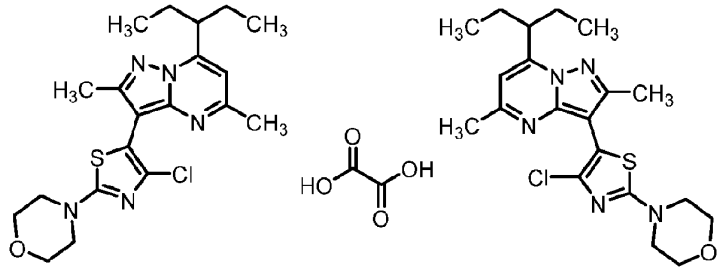
[0013] In some aspects, the present disclosure provides a pharmaceutical composition comprising Compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition comprising Compound 1 is a crystalline pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises crystalline Compound 1.

[0014] In another aspect, the present disclosure provides a method of preparing a crystalline composition comprising Compound 1 (e.g., comprising Formula I:



Formula I,

wherein the method comprises:

a) dissolving 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) and oxalic acid in a solvent;

(b) heating the solution or slurry from step (a); and

(c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0015] In some embodiments of the method of preparing the crystalline composition comprising Compound I (e.g., comprising Formula I), the solvent in step (a) comprises acetone, heptane, water, 2-butanol, ethyl acetate, 2-propanol, methyl tert-butyl ether, ethanol, methyl ethyl ketone, 1-pentanol, or a combination thereof. In some embodiments, the solvent in step (a) is heptane. In some embodiments, the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone. In some embodiments, the solvent in step (a) is a mixture of heptane and methyl ethyl ketone. In some embodiments, step (b) is heated at about 50 °C.

[0016] In another aspect, the present disclosure provides a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the subject has congenital adrenal hyperplasia (CAH).

[0017] In another aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the CAH is a classic CAH. In some embodiments, the CAH is a non-classical CAH.

[0018] In another aspect, the present disclosure provides a method of improving (e.g., lessening the severity and/or frequency) hyperandrogenic symptoms in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism, amenorrhea, and alopecia.

[0019] In another aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

[0020] In another aspect, the present disclosure provides a method of improving (e.g., lessening the severity and/or frequency) metabolic symptoms in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the metabolic symptoms are

selected from the group consisting of body weight, BMI, fat mass, waist circumference, blood pressure and glycemic control. Metabolic symptoms may be evaluated using an assessment, such as, for example, fasting lipid panel, homeostatic model assessment of insulin resistance [HOMA-IR] based on fasting glucose and insulin levels, glycated hemoglobin [HbAlc], glucose tolerance test.

[0021] In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

[0022] In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

[0023] In another aspect, the present disclosure provides a method of treating endometriosis or improving the symptoms of endometriosis in a subject in need thereof, comprising administering to the subject a crystalline composition comprising Formula I as described herein, the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein, or the pharmaceutical composition comprising Compound 1 as described herein. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition improves the symptom of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition reduces the symptoms of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition prevents or lowers the perception of pain experienced by the subject (e.g., as measured on a pain scale). In some embodiments, the administration of the crystalline composition or the pharmaceutical composition eliminates the perception of pain experienced by the subject.

[0024] In various embodiments of the methods as described herein, the crystalline composition or the pharmaceutical composition is administered at a dose from about 5

mg/day to about 1000 mg/day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fed state. A fed state may mean that the subject has eaten within a 30-minute period before of receiving the crystalline composition or the pharmaceutical compositions. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fasted state. A fasted state may mean that the subject has not eaten within a 30-minute period before of receiving the crystalline composition or the pharmaceutical compositions. In some embodiments, the crystalline composition or the pharmaceutical composition is administered at least once per day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered once a day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered twice a day.

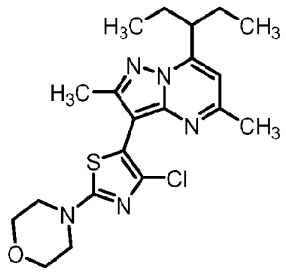
[0025] In various embodiments of the methods as described herein, the method further comprises administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen agent. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone. In some embodiments, the additional therapeutic agent is a different CRF1 antagonist.

[0026] In various embodiments of the methods as described herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, or the pharmaceutical composition comprising the crystalline composition as described herein. In some embodiments, the additional therapy is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, the pharmaceutical composition comprising the crystalline composition as described herein, or the pharmaceutical composition comprising Compound 1 as described herein.

[0027] In various embodiments of the methods, the subject is from about 9 years of age to about 18 years of age. In some embodiments, the subject is from about 8 years of age to about 55 years of age.

[0028] In additional aspects, provided herein is a pharmaceutical composition comprising a CRF1 antagonist, wherein the composition is characterized by an X-ray powder diffraction

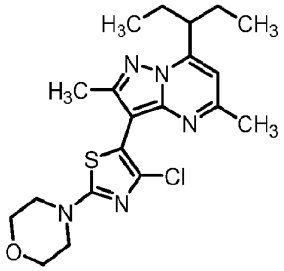
pattern comprising a peak selected from any one or more of 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the composition is characterized by X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from 5.44 ± 0.2° 2-θ, 20.78 ± 0.2° 2-θ, 22.74 ± 0.2° 2-θ, 23.04 ± 0.2° 2-θ, 26.80 ± 0.2° 2-θ, and 28.86 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least five peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the CRF1 antagonist comprises Compound 1:



Compound 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is a crystalline pharmaceutical composition. In some embodiments, the crystalline pharmaceutical composition further comprises oxalic acid. In some embodiments, the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1.

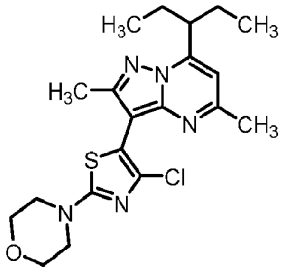
[0029] In additional aspects, provided herein is a pharmaceutical composition comprising a CRF1 antagonist, wherein the pharmaceutical com-position is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C. In some embodiments, the pharmaceutical composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset

of about 164 °C and a peak of about 166 °C. In some embodiments, the pharmaceutical composition is characterized by a melting point of about 166 °C. In some embodiments, the CRF1 antagonist comprises Compound 1:



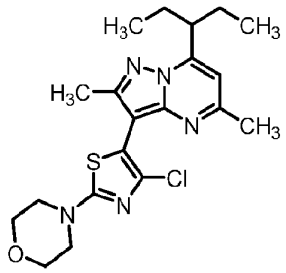
[0030] Compound 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is a crystalline pharmaceutical composition. In some embodiments, the crystalline pharmaceutical composition further comprises oxalic acid. In some embodiments, the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1. In some embodiments, the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C.

[0031] In additional aspects, provided herein is method of preparing a crystalline composition comprising Compound 1:



Compound 1, wherein the method comprises: (a) dissolving Compound 1 and an acid in a solvent; (b) heating the solution or slurry from step (a); and (c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound 1. In some embodiments, the acid comprises oxalic acid. In some embodiments, the solvent in step (a) is heptane. In some embodiments, the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone. In some embodiments, the solvent in step (a) is a mixture of heptane and methyl ethyl ketone. In some embodiments, step (b) is heated at about 50 °C.

[0032] In additional aspects, further provided herein is a pharmaceutical composition comprising Compound 1:



Compound 1, or a pharmaceutically acceptable salt or solvate thereof, wherein Compound 1 is present in an amount of 25% w/w; and a diluent in about 5% to about 70% In some embodiments, Compound 1 is in an amount of about 50 mg to about 200 mg. In some embodiments, Compound 1 is in an amount of about 50 mg. In some embodiments, wherein the diluent is selected from the group consisting of calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose monohydrate, and a combination thereof. In some embodiments, the diluent is lactose monohydrate. In some embodiments, the lactose monohydrate is about 20% to about 45% by weight of the pharmaceutical composition. In some embodiments, the lactose monohydrate is about 20% to about 40.25% by weight of the pharmaceutical composition. In some embodiments, the lactose monohydrate is in an amount that is about 16.1, 40.25, 80.5, or 322 mg. In some embodiments, the diluent is microcrystalline cellulose. In some embodiments, the pharmaceutical composition further comprises a second diluent, wherein the second diluent comprises microcrystalline cellulose. In some embodiments, the microcrystalline cellulose is about 25% by weight of the pharmaceutical composition. In some embodiments, the microcrystalline cellulose is in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition further comprises a binder, wherein the binder is selected from the group consisting of corn starch and potato starch, gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC), and a combination thereof. In some embodiments, the binder comprises HPC. In some embodiments, the HPC is about 3% by weight of the solid dosage form. In some embodiments, the pharmaceutical composition further comprises a surfactant, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate, tetradecyl trimethyl ammonium bromide with dodecyl, hexadecyl compound, benzalkonium chloride, cetylpyridinium chloride, alkylsulphate, alkylethoxylate sulphate, soap, carxylate ion, sulfate

ion, sulfonate ion, polyoxyethylene derivative, polyoxypropylene derivative, polyol derivative, polyol ester, polyoxyethylene ester, poloxamers, glocol, glycerol ester, sorbitan derivative, and polyethylene glycol, and a combination thereof. In some embodiments, the surfactant comprises sodium lauryl sulfate. In some embodiments, the sodium lauryl sulfate is about 0.75% by weight of the solid dosage form. In some embodiments, the sodium lauryl sulfate is in an amount that is about 1.5 mg. In some embodiments, the pharmaceutical composition further comprises a disintegrant, wherein the disintegrant is selected from the group consisting of starch, alginic acid, ac-di-sol, croscarmellose sodium, sodium starch glycolate, and crospovidone, and a combination thereof. In some embodiments, the disintegrant comprises croscarmellose sodium.

[0033] In some embodiments, the pharmaceutical composition further comprises a glidant, wherein the glidant comprises colloidal silicon dioxide. In some embodiments, the colloidal silicon dioxide is about 1% by weight of the solid dosage form. In some embodiments, the colloidal silicon dioxide is in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition further comprises a lubricant, wherein the lubricant is selected from the group consisting of talc, stearic acid, magnesium stearate, sodium stearyl fumarate, and a combination thereof. In some embodiments, the pharmaceutical formulation is in a solid dosage form. In some embodiments, the solid dosage form is a tablet. In some embodiments, the solid dosage form is a granules form. In some embodiments, said granules form is packaged in a capsule. In some embodiments, said granules form is packaged in a sachet.

[0034] In additional aspects, provided herein is a pharmaceutical formulation, comprising: (a) about 10 mg to about 300 mg of 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-α) pyrimidine (Compound 1), or a pharmaceutically acceptable salt or solvate thereof; (b) a first diluent in about 40% to about 45% by weight, wherein the first diluent comprises lactose monohydrate; (c) a second diluent in about 25% by weight, wherein the second diluent comprises microcrystalline cellulose; (d) about 1% to about 6% by weight of hydroxypropyl cellulose; (e) about 0.5% to about 5% by weight of sodium lauryl sulfate; and (f) about 4% by weight of croscarmellose sodium.

DESCRIPTION OF THE DRAWINGS

[0035] The novel features of the present disclosure are set forth with particularity in the appended claims. An understanding of the features and advantages of the present disclosure may be obtained by reference to the following detailed description that sets forth illustrative

embodiments, in which the principles of the present disclosure are utilized, and the accompanying drawings of which:

[0036] FIG. 1 shows the X-ray powder diffraction (XRPD) pattern for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0037] FIG. 2 shows the differential scanning calorimetry (DSC) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0038] FIG. 3 shows the thermogravimetric analysis (TGA) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0039] FIG. 4 shows the dynamic vapor sorption (DVS) trace for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0040] FIG. 5 shows the infrared (IR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0041] FIG. 6 shows the proton nuclear magnetic resonance (^{1}H NMR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0042] FIG. 7 shows the Raman spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

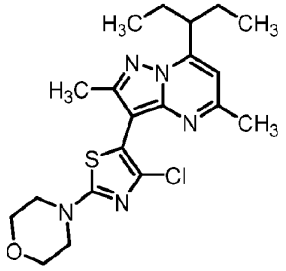
DETAILED DESCRIPTION

[0043] 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) is a potent antagonist of Corticotropin-releasing hormone receptor 1 (CRF1). CRF1 antagonists may be useful in the treatment of various diseases, conditions, and disorders for which abnormal CRF1 activity plays a role.

[0044] Crystalline forms of a small molecule drug candidate, such as a CRF1 antagonist, may have different physical properties, including melting point, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties may have an effect on the ability to process or manufacture a drug substance and the drug product. Moreover, differences in these properties can and often lead to different pharmacokinetics profiles for different polymorphic forms of a drug. Polymorphism may affect the quality, safety, and/or efficacy of a drug product, such as a CRF1 antagonist. Thus, there still remains a need for crystalline compositions of CRF1 antagonist. The present disclosure addresses this need and provides related advantages as well.

Compound 1

[0045] As described herein, Compound 1 refers to 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine, which has the chemical structure as shown below:



Compound 1.

[0046] Compound 1 is a CRF1 modulator. CRF1 modulator, such as a CRF1 antagonist or inhibitor, are useful in the treatment of various conditions and disorders that are mediated by CRF1 activities.

[0047] In some embodiments, the present disclosure provides a crystalline composition comprising Compound 1. In some embodiments, the crystalline composition comprises Compound 1 and a weak acid (e.g., oxalic acid) (e.g., in a molar ratio of 2:1). In some embodiments, the crystalline composition comprises Compound 1 and an acid in a molar ratio of 2:1. In some embodiments, the crystalline composition comprises Compound 1 and an acid in a molar ratio of 1:1.

[0048] As used herein, "crystalline," "crystalline form," "polymorph," "Form," and "form" may be used interchangeably herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, co-crystals, polymorphs, pseudopolymorphs, salts, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. Compounds of the present disclosure include crystalline and amorphous forms of those compounds, including, for example, polymorphs, co-crystals, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[0049] As used herein, "co-crystal" may be used to describe crystalline compositions comprising multi-component crystals based on hydrogen bonding interactions of hydrogen ions to form salt forms. In some embodiments, the crystalline composition as described

herein are co-crystals comprising an acid (e.g., a weak acid (e.g., oxalic acid)) and Compound 1.

Definitions

[0050] A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative, such as those known in the art, for example, described in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

[0051] As used herein, "treating" and like terms refer to reducing the severity and/or frequency of symptoms, eliminating symptoms and/or the underlying cause of said symptoms, reducing the frequency or likelihood of symptoms and/or their underlying cause, delaying, preventing and/or slowing the progression of diseases and/or disorders and improving or remediating damage caused, directly or indirectly, by the diseases and/or disorders.

[0052] As used herein, "delaying development of a disease" or the like, means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease (such as cancer) or a sign or symptom of the disease. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease. For example, a late stage cancer, such as development of metastasis, may be delayed.

[0053] As used herein, an "effective dosage" or "effective amount" of drug, compound, or pharmaceutical composition is an amount sufficient to effect beneficial or desired results. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, delaying development of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. In the case of cancer or tumor, an effective amount of the drug may have the effect in reducing the number of cancer cells;

reducing the tumor size; inhibiting (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibiting, to some extent, tumor growth; and/or relieving to some extent one or more of the symptoms associated with the disorder. An effective dosage can be administered in one or more administrations. For purposes of this invention, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an "effective dosage" may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0054] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. Inhibition may refer to reduction of a disease or symptoms of disease. Inhibition may refer to a reduction in the activity of a particular protein or nucleic acid target. The protein may be deoxycytidine kinase. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein.

[0055] The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule.

[0056] The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, a modulator of a target protein changes by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. A modulator of a disease decreases a symptom, cause, or characteristic of the targeted disease.

[0057] "Selective" or "selectivity" or the like of a compound refers to the compound's ability to discriminate between molecular targets.

[0058] "Specific", "specifically", "specificity", or the like of a compound refers to the compound's ability to cause a particular action, such as inhibition, to a particular molecular target with minimal or no action to other proteins in the cell.

[0059] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0060] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0061] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc.

[0062] By "co-administer" it is meant that a compound described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example, an anticancer agent as described herein. The compounds described

herein can be administered alone or can be co-administered to the patient. Co-administration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. anticancer agents).

[0063] Co-administration includes administering one active agent (e.g. Compound 1 described herein) within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent (e.g. anti-cancer agents). Also contemplated herein, are embodiments, where co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. Co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In some embodiments, the active and/or adjunctive agents are linked or conjugated to one another. In some embodiments, the compounds described herein are combined with treatments for cancer such as chemotherapy or radiation therapy.

[0064] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease means that the disease is caused by (in whole or in part), a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function, or a side-effect of the compound (e.g. toxicity) is caused by (in whole or in part) the substance or substance activity or function.

[0065] "Patient," "subject," "patient in need thereof," and "subject in need thereof" are herein used interchangeably and refer to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human. A "cancer-patient" is a patient suffering from, or prone to developing cancer.

[0066] Unless clearly indicated otherwise, the term "individual" as used herein refers to a mammal, including but not limited to, bovine, horse, feline, rabbit, canine, rodent, or primate (e.g., human). In some embodiments, an individual is a human. In some embodiments, an individual is a non-human primate such as chimpanzees and other apes and monkey species. In some embodiments, an individual is a farm animal such as cattle, horses, sheep, goats and swine; pets such as rabbits, dogs and cats; laboratory animals including rodents, such as rats,

mice, and guinea pigs; and the like. In some embodiments, the invention find use in both human medicine and in the veterinary context.

[0067] "Disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. In some embodiments, the disease as used herein refers to cancer.

[0068] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly indicates otherwise.

[0069] The term "about" when used in reference to numerical ranges, cut-offs, or specific values is used to indicate that the recited values may vary by up to as much as 10% from the listed value. As many of the numerical values used herein are experimentally determined, it should be understood by those skilled in the art that such determinations can, and often times will, vary among different experiments. The values used herein should not be considered unduly limiting by virtue of this inherent variation. Thus, the term "about" is used to encompass variations of ±10% or less, variations of ±5% or less, variations of ±1% or less, variations of ±0.5% or less, or variations of ±0.1% or less from the specified value.

[0070] It is understood that aspect and variations of the invention described herein include "consisting" and/or "consisting essentially of" aspects and variations.

Crystalline Composition Comprising Compound I (e.g., Comprising Formula I)

[0071] The crystalline composition prepared according to the methods of the present disclosure may be characterized by any methodology comprising the art. For example, the crystalline composition comprising Compound 1 ((e.g., comprising Formula I) e.g., prepared comprising the methods of the present disclosure)) may be characterized by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and/or spectroscopy (e.g., Raman, solid state nuclear magnetic resonance (ssNMR), proton nuclear magnetic resonance (^{1}H NMR), and infrared (IR)). In some embodiments, crystallinity of the solid form is determined by X-Ray Powder Diffraction (XPRD).

[0072] Formula 1 may represent a composition comprising two molecules of Compound 1 and one molecules of oxalic acid. As such, Formula I may represent a molar ratio of Compound 1 to oxalic acid in a ratio of about 2:1.

[0073] XRPD: Crystalline composition according to the present disclosure may be characterized by XRPD (e.g., crystalline composition(s) comprising the present disclosure can also be identified by its characteristic XRPD peaks, such as show in FIG. 1). The relative intensities of XRPD peaks may vary, depending upon the particle size, the sample

preparation technique, the sample mounting procedure and the particular instrument employed. Moreover, instrument variation and other factors may affect the 2-θ values. Therefore, the XRPD peak assignments may vary, for example by plus or minus about 0.2 degrees.

[0074] DSC: Crystalline composition according to the present disclosure can also be identified by its characteristic DSC thermograms such as shown in FIG. 2. For DSC, it is known that the temperatures observed may depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms may vary, for example by plus or minus about 4°C.

[0075] TGA: Crystalline composition according to the present disclosure may also give rise to thermal behavior different from that of the amorphous material or other crystalline forms. Thermal behavior may be measured in the laboratory by thermogravimetric analysis (TGA) which may be used to distinguish some crystalline forms from others. In one aspect, the crystalline composition as described herein may be characterized by thermogravimetric analysis.

[0076] DVS: Crystalline composition comprising the present disclosure may also give rise to vapors sorption behavior different from that of the amorphous material or other crystalline forms. The vapor sorption behavior may be measured in the laboratory by dynamic vapor sorption (DVS) which may be used to distinguish some crystalline forms from others. In one aspect, the crystalline composition as described herein may be characterized by dynamic vapor sorption.

[0077] The crystalline composition comprising Compound 1 (e.g. comprising Formula I) may be useful in the production of medicinal preparations and can be obtained by means of a crystallization process to produce crystalline and semi-crystalline forms or a solidification process to obtain the amorphous form. In some embodiments, the crystallization is carried out by either generating the desired compound (for example Compound 1) in a reaction mixture and isolating the desired crystalline composition from the reaction mixture, or by dissolving raw compound (e.g., Compound 1) in a solvent, optionally with heat, followed by crystallizing/solidifying the product by cooling (including active cooling) and/or by the addition of an antisolvent for a period of time. The crystallization or solidification may be followed by drying carried out under controlled conditions until the desired water content is reached in the end crystalline composition.

[0078] FIG. 1 shows the X-ray powder diffraction (XRPD) pattern for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0079] FIG. 2 shows the differential scanning calorimetry (DSC) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0080] FIG. 3 shows the thermogravimetric analysis (TGA) thermogram for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

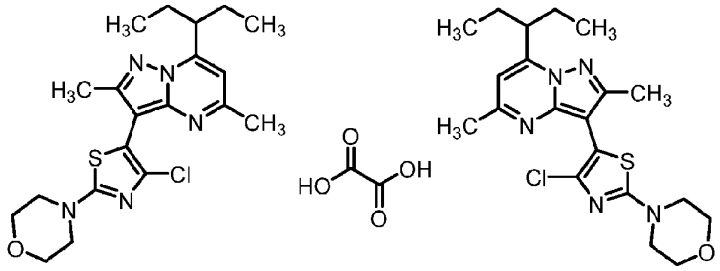
[0081] FIG. 4 shows the dynamic vapor sorption (DVS) trace for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0082] FIG. 5 shows the infrared (IR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0083] FIG. 6 shows the proton nuclear magnetic resonance (^{1}H NMR) spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0084] FIG. 7 shows the Raman spectrum for the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[0085] In some aspects, the present disclosure provides a crystalline composition comprising Compound 1. In some embodiments the crystalline composition comprising Compound 1 is a crystalline composition comprising Formula I:



Formula I.

[0086] In some embodiments, Formula I represents Compound 1 and oxalic acid in a molar ratio of 2:1.

[0087] In some embodiments, the crystals of the crystalline composition comprising Compound 1 (e.g., comprising Formula I) has unit cell parameters at T = 150°K of: a = 34.003(4) Å, b = 6.5843(13) Å, c = 21.062(5) Å; β = 108.703(12)°, V = 4466.5(15) Å^3 and a monoclinic C2/c space group.

[0088] In some embodiments, the crystals of a composition (e.g., a crystalline composition comprising Compound 1 (e.g., comprising Formula I)) is characterized by:

(a) an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å;

(b) an X-ray powder diffraction pattern substantially the same as shown in FIG. 1;

(c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C;

(d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C;

(e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2;

(f) a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C;

(g) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3; or

(h) combinations thereof.

[0089] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., v Formula I)) is characterized by an X-ray powder diffraction pattern comprising any one or more peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the XRPD pattern comprises at least one of the aforementioned peaks (10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å). In some embodiments, the XRPD pattern comprises at least two of the aforementioned peaks. In some embodiments, the XRPD pattern comprises at least three of the aforementioned peaks. In some embodiments, the XRPD pattern comprises at least four of the aforementioned peaks. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I) is characterized by an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.1° 2-θ, 15.96 ± 0.1° 2-θ, 23.44 ± 0.1° 2-θ, and 24.80 ± 0.1° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I) is characterized by an X-ray powder diffraction pattern comprising peaks at about 10.84° 2-θ, about 15.96° 2-θ, about 23.44° 2-θ, and about 24.80° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

[0090] In some embodiments, the X-ray powder diffraction (XRPD) pattern further comprising at least one peak selected from 5.44 ± 0.2° 2-θ, 20.78 ± 0.2° 2-θ, 22.74 ± 0.2° 2-θ, 23.04 ± 0.2° 2-θ, 26.80 ± 0.2° 2-θ, and 28.86 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from 5.44 ± 0.1° 2-θ, 20.78 ± 0.1° 2-θ, 22.74 ± 0.1° 2-θ, 23.04 ± 0.1° 2-θ, 26.80 ± 0.1° 2-θ, and 28.86 ± 0.1° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from about 5.44° 2-θ, about 20.78° 2-θ, about 22.74° 2-θ, about 23.04° 2-θ, about 26.80° 2-θ, and about 28.86° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

[0091] In some embodiments, the X-ray powder diffraction pattern further comprising at least one peak selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least two peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least three peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least four peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least five peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2°

2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least six peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least seven peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern further comprising at least eight peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks selected from 8.82 ± 0.1° 2-θ, 11.70 ± 0.1° 2-θ, 14.60 ± 0.1° 2-θ, 15.56 ± 0.1° 2-θ, 16.70 ± 0.1° 2-θ, 18.82 ± 0.1° 2-θ, 19.18 ± 0.1° 2-θ, 20.02 ± 0.1° 2-θ, 20.50 ± 0.1° 2-θ, 21.72 ± 0.1° 2-θ, 25.52 ± 0.1° 2-θ, 25.92 ± 0.1° 2-θ, 26.94 ± 0.1° 2-θ, and 28.00 ± 0.1° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks selected from 8.82° 2-θ, 11.70° 2-θ, 14.60° 2-θ, 15.56° 2-θ, 16.70° 2-θ, 18.82° 2-θ, 19.18° 2-θ, 20.02° 2-θ, 20.50° 2-θ, 21.72° 2-θ, 25.52° 2-θ, 25.92° 2-θ, 26.94° 2-θ, and 28.00° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

[0092] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C. In some embodiments, the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C. In some embodiments, the crystalline composition is characterized by a melting point of about 166 °C. In some embodiments, the

crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2.

[0093] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 160 °C to about 170 °C, about 160 °C to about 169 °C, about 160 °C to about 168 °C, about 160 °C to about 167 °C, about 160 °C to about 166 °C, about 160 °C to about 165 °C, about 160 °C to about 164 °C, about 160 °C to about 163 °C, about 160 °C to about 162 °C, about 160 °C to about 161 °C, about 161 °C to about 170 °C, about 162 °C to about 170 °C, about 163 °C to about 170 °C, about 164 °C to about 170 °C, about 165 °C to about 170 °C, about 166 °C to about 170 °C, about 167 °C to about 170 °C, about 168 °C to about 170 °C, or about 169 °C to about 170 °C. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 162 °C to about 166 °C, for example at about 162 °C, about 163 °C, about 164 °C, 165 °C, or 166 °C. In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., (e.g., comprising Compound 1))) is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm at about 164 °C. In some embodiments, the crystalline composition according for Formula I has a melting point of about 166 °C.

[0094] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C. In some embodiments, the crystalline composition decomposes above a temperature of about 50 °C, about 100 °C, about 150 °C, about 200 °C, about 250 °C, about 300 °C, about 350 °C, or about 400 °C. In some embodiments, the crystalline composition decomposes above a temperature of about 200 °C. In some embodiments, the crystalline composition decomposes above a temperature of about 250 °C. In some embodiments, the crystalline composition is characterized by a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3.

[0095] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is characterized by a dynamic vapor sorption (DVS) trace substantially the same as shown in FIG. 4.

[0096] In some embodiments, the composition (e.g., crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I))) is anhydrous.

[0097] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is stable at room temperature. In some examples, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) can be stored at room temperature for an extended period of time without significant chemical degradation or change in the crystalline form. In some examples, crystalline composition comprising Compound 1 (e.g., comprising Formula I) can be stored at room temperature for a timer period of at least about 10 days, 30 days, 60 days, 90 days, 120 days, 150 days, or 180 days. In some examples, the crystalline composition can be stored at room temperature for a time period of more than about 180 days. In some examples, the crystalline composition can be stored at room temperature for a time period of 10-14 days, 10-18 days, 10-22 days, 10-26 days, 10-30 days, 10-40 days, 10-50 days, 10-60 days, 10-90 days, 10-120 days, 10-150 days, 10-180 days, 14-18 days, 14-22 days, 14-26 days, 14-30 days, 14-40 days, 14-50 days, 14-60 days, 14-90 days, 14-120 days, 14-150 days, 14-180 days, 18-22 days, 18-26 days, 18-30 days, 18-40 days, 18-50 days, 18-60 days, 18-90 days, 18-120 days, 18-150 days, 18-180 days, 22-26 days, 22-30 days, 22-40 days, 22-50 days, 22-60 days, 22-90 days, 22-120 days, 22-150 days, 22-180 days, 26-30 days, 26-40 days, 26-50 days, 26- 60 days, 26-90 days, 26-120 days, 26-150 days, 26-180 days, 30-40 days, 30-50 days, 30-60 days, 30-90 days, 30-120 days, 30-150 days, 30-180 days, 40-50 days, 40-60 days, 40-90 days, 40-120 days, 40-150 days, 40-180 days, 50-60 days, 50-90 days, 50-120 days, 50-150 days, 50-180 days, 60-90 days, 60-120 days, 60-150 days, 60-180 days, 90-120 days, 90-150 days, or 90-180 days. In some examples, the crystalline composition can be stored at room temperature for a time period of at least 10 days, 14 days, 18 days, 22 days, 26 days, 30 days, 40 days, 50 days, 60 days, 90 days, 120 days, 150 days, or 180 days.

[0098] In some embodiments, the crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) is stable at room temperature or temperatures above the room temperature and/or at high relative humidity (RH) (e.g., accelerated aging conditions or long-term storage conditions). In some embodiments, the crystalline composition is stable for at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, at least twelve months, at least fourteen months, at least sixteen months, and at least eighteen months. In some examples, the crystalline composition can be stored at about 25 °C and at about 75%

RH for an extended period of time without significant chemical degradation or change in the crystalline form. In some examples, the crystalline composition comprising a CRF1 antagonist (e.g., Compound 1 (e.g., comprising Formula I)) can be stored at about 25 °C and at about 75% RH for a time period of at least about 10 days, 30 days, 60 days, 90 days, 120 days, 150 days, or 180 days. In some examples, the crystalline composition can be stored at about 25 °C and at about 75% RH for a time period of 10-14 days, 10-18 days, 10-22 days, 10-26 days, 10-30 days, 10-40 days, 10-50 days, 10-60 days, 10-90 days, 10-120 days, 10-150 days, 10-180 days, 14-18 days, 14-22 days, 14-26 days, 14-30 days, 14-40 days, 14-50 days, 14-60 days, 14-90 days, 14-120 days, 14-150 days, 14-180 days, 18-22 days, 18-26 days, 18-30 days, 18-40 days, 18-50 days, 18-60 days, 18-90 days, 18-120 days, 18-150 days, 18-180 days, 22-26 days, 22-30 days, 22-40 days, 22-50 days, 22-60 days, 22-90 days, 22-120 days, 22-150 days, 22-180 days, 26-30 days, 26-40 days, 26-50 days, 26- 60 days, 26-90 days, 26-120 days, 26-150 days, 26-180 days, 30-40 days, 30-50 days, 30-60 days, 30-90 days, 30-120 days, 30-150 days, 30-180 days, 40-50 days, 40-60 days, 40-90 days, 40-120 days, 40-150 days, 40-180 days, 50-60 days, 50-90 days, 50-120 days, 50-150 days, 50-180 days, 60-90 days, 60-120 days, 60-150 days, 60-180 days, 90-120 days, 90-150 days, or 90-180 days. In some examples, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) can be stored at about 25 °C for a time period of at least 10 days, 14 days, 18 days, 22 days, 26 days, 30 days, 40 days, 50 days, 60 days, 90 days, 120 days, 150 days, or 180 days.

[0099] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is thermodynamically stable.

[00100] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is highly bioavailable.

[00101] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is stable under accelerated storage conditions.

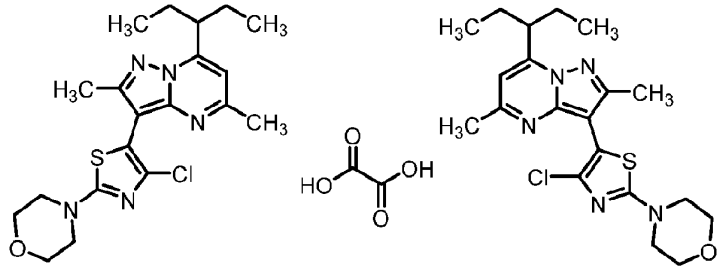
[00102] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is characterized by an infrared (IR) spectrum substantially the same as shown in FIG. 5.

[00103] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is characterized by a proton nuclear magnetic resonance (^{1}H NMR) spectrum substantially the same as shown in FIG. 6.

[00104] In some embodiments, the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is characterized by a Raman spectrum substantially the same as shown in FIG. 7.

Compositions and Formulations

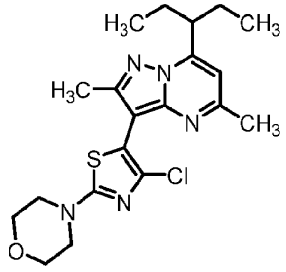
[00105] In some aspects, the present disclosure provides a pharmaceutical composition comprising a crystalline composition comprising Formula I:



Formula I,

and at least one pharmaceutically acceptable carrier or excipient.

[00106] In some aspects, the present disclosure provides a pharmaceutical composition comprising Compound 1:



Compound 1,

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition is a crystalline pharmaceutical composition comprising Compound 1. In some embodiments, the crystalline pharmaceutical composition comprising Compound 1 comprises Formula I.

Dosage Form

[00107] In some embodiments, the pharmaceutical composition described herein is provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of the crystalline composition comprising Compound 1 (e.g., comprising Formula I)

that is suitable for administration to a subject in a single dose. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

[00108] In some embodiments, the pharmaceutical compositions described herein are formulated as oral dosage forms. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules. In some embodiments, the pharmaceutical composition comprises one or more additional pharmaceutically acceptable excipients. See, e.g., Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005) for a list of pharmaceutically acceptable excipients.

Capsule

[00109] In some embodiments, the pharmaceutical composition comprising the crystalline composition comprising Compound 1 (e.g., comprising Formula I) is formulated as a capsule. In some embodiments, the pharmaceutical composition is encapsulated in a hard gel capsule. In some embodiments, the pharmaceutical composition is encapsulated in a soft gel capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

[00110] In some embodiments, the pharmaceutical composition comprising Compound 1 is formulated as a capsule. In some embodiments, the pharmaceutical composition is encapsulated in a hard gel capsule. In some embodiments, the pharmaceutical composition is encapsulated in a soft gel capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

[00111] In some embodiments, the capsule is formed using materials which include, but are not limited to, natural or synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, or any combinations thereof. In some embodiments, the capsule is formed using preservatives, coloring and opacifying agents, flavorings and sweeteners, sugars, gastroresistant substances, or any combinations thereof. In some embodiments, the capsule is coated. In some embodiments, the coating covering the capsule includes, but is not limited to, immediate release coatings, protective coatings, enteric or delayed release coatings, sustained release coatings, barrier coatings, seal

coatings, or combinations thereof. In some embodiments, a capsule herein is hard or soft. In some embodiments, the capsule is seamless. In some embodiments, the capsule is broken such that the particulates are sprinkled on soft foods and swallowed without chewing. In some embodiments, the shape and size of the capsule also vary. Examples of capsule shapes include, but are not limited to, round, oval, tubular, oblong, twist off, or a non-standard shape. The size of the capsule may vary comprising the volume of the particulates. In some embodiments, the size of the capsule is adjusted based on the volume of the particulates and powders. Hard or soft gelatin capsules may be manufactured in accordance with conventional methods as a single body unit comprising the standard capsule shape. A single-body soft gelatin capsule typically may be provided, for example, in sizes from 3 to 22 minims (1 minims being equal to 0.0616 ml) and in shapes of oval, oblong or others. The gelatin capsule may also be manufactured in accordance with conventional methods, for example, as a two-piece hard gelatin capsule, sealed or unsealed, typically in standard shape and various standard sizes, conventionally designated as (000), (00), (0), (1), (2), (3), (4), and (5). The largest number corresponds to the smallest size. In some embodiments, the pharmaceutical composition described herein (e.g., capsule) is swallowed as a whole.

[00112] In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients.

[00113] In some embodiments, the capsule is free of additional excipients.

Tablet

[00114] In some embodiments, the pharmaceutical composition comprising the crystalline composition comprising Compound I (e.g., comprising Formula I) is formulated as a tablet.

[00115] In some embodiments, the pharmaceutical composition comprising Compound 1 is formulated as a tablet.

[00116] In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg or less than about 200 mg. In some embodiments, the tablet has a dose strength of more than about 50 mg, more than about 100 mg, more than about 150 mg, more than about 200 mg, or more than about 250 mg. In some embodiments, the tablet size is less than about 1000 mg for a dose strength of more than about 50 mg. In some embodiments, the tablet size is less than 800 mg for a dose strength of more than about 100 mg. In some embodiments, the tablet size is less than 600 mg for a dose strength of more than about 150 mg. In some embodiment, the tablet size is less than 400 mg for a dose strength of more than about 200 mg. In some embodiments, the tablet size is less

than 400 mg for a dose strength of 200 mg. In some embodiments, the tablet size is about 200 mg for a dose strength of about 50 mg.

[00117] In some embodiments, more than about 20% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 24 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 12 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 6 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 3 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 2 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than 70% of the tablet is dissolved in 60 minutes in conventional dissolution media.

[00118] In some embodiments, the tablet is produced at a commercial scale.

[00119] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[00120] In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete

dry powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of Compound 1. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone, polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

Oral dosage forms

[00121] In some embodiments, the pharmaceutical composition comprising Compound 1 or the crystalline composition comprising Formula I or is formulated as an oral dosage form. In some embodiments, the oral dosage form is selected from the group consisting of a tablet, a capsule, a buccal tablet, a sub-lingual table, an orally-disintegrating tablet, a thin film, a liquid solution, a liquid suspension, a syrup, a powder, and solid crystals. In some embodiment, the oral dosage form is selected from the group consisting of a tablet, a capsule, a buccal tablet, a sub-lingual table, an orally-disintegrating tablet, a thin film, a liquid solution, a liquid suspension, a syrup, a powder, solid crystals, minitabs, coated pellets and sachets.

[00122] Oral dosage forms may include capsules, tablets, pills, powders or granules. Such forms may include forms that dissolve or disintegrate quickly in the oral environment. Such forms may be prepared with coatings and shells. In some embodiments, these oral dosage forms are capable of controlled or sustained release.

Pharmaceutically Acceptable Excipients

[00123] In some embodiments, the pharmaceutical composition comprising Compound 1 (e.g., crystalline composition comprising Compound 1) or the crystalline composition comprising Formula I comprises a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is free of pharmaceutically acceptable excipients. The term "pharmaceutically acceptable excipient", as used herein, means one or more compatible solid or encapsulating substances, which are suitable for administration to a

mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction, which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. In some embodiments, the pharmaceutically acceptable excipient is of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal, being treated.

[00124] Some examples of substances, which can serve as pharmaceutically acceptable excipients include:

- Amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, the amino acid is arginine. In some embodiments, the amino acid is L-arginine.
- Monosaccharides such as glucose (dextrose), arabinose, mannitol, fructose (levulose), and galactose.
- Cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose.
- Solid lubricants such as talc, stearic acid, magnesium stearate and sodium stearyl fumarate.
- Polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol.
- Emulsifiers such as the polysorbates.
- Wetting agents such as sodium lauryl sulfate, Tween®, Span , alkyl sulphates, and alkyl ethoxylate sulphates.
- Cationic surfactants such as cetrimide, benzalkonium chloride, and cetylpyridinium chloride.
- Diluents such as calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose.
- Binders such as starches (corn starch and potato starch), gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC).
- Disintegrants such as starch, and alginic acid.
- Super-disintegrants such as ac-di-sol, croscarmellose sodium, sodium starch glycolate and crospovidone.

- Glidants such as silicon dioxide.
- Coloring agents such as the FD&C dyes.
- Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors.
- Preservatives such as benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate, phenylmercuric nitrate, parabens, and sodium benzoate.
- Tonicity adjustors such as sodium chloride, potassium chloride, mannitol, and glycerin.
- Antioxidants such as sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA.
- pH adjuster such as NaOH, sodium carbonate, sodium acetate, HCl, and citric acid.
- Cryoprotectants such as sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran.
- Surfactants such as sodium lauryl sulfate. For example, cationic surfactants such as cetrimide (including tetradecyl trimethyl ammonium bromide with dodecyl and hexadecyl compounds), benzalkonium chloride, and cetylpyridinium chloride. Some examples of anionic surfactants are alkylsulphates, alkylethoxylate sulphates, soaps, carboxylate ions, sulfate ions, and sulfonate ions. Some examples of non-ionic surfactants are polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glocol, glycerol esters, sorbitan derivatives, polyethylene glycol (such as PEG-40, PEG-50, or PEG-55) and esters of fatty alcohols.
- Organic materials such as carbohydrates, modified carbohydrates, lactose (including a-lactose, monohydrate spray dried lactose or anhydrous lactose), starch, pregelatinized starch, sucrose, mannitol, sorbital, cellulose (including powdered cellulose and microcrystalline cellulose).
- Inorganic materials such as calcium phosphates (including anhydrous dibasic calcium phosphate, dibasic calcium phosphate or tribasic calcium phosphate).
- Co-processed diluents.
- Compression aids.
- Anti-tacking agents such as silicon dioxide and talc.

[00125] In some embodiments, the pharmaceutical composition comprises the crystalline composition comprising Formula I.

[00126] In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprises Compound 1.

[00127] In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 95% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 90% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 85% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 80% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 70% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 65% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% to about 20% by weight of the dosage form.

[00128] In some embodiments, the pharmaceutical composition comprises a diluent in about 95% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 90% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 85% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 80% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 70% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 65% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises

a diluent in about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 20% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a diluent in about 5% by weight of the dosage form.

[00129] In some embodiments, the pharmaceutical composition comprises a second diluent. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 95% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 90% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 85% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 80% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 70% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 65% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 40% by weight of the dosage

form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% to about 20% by weight of the dosage form.

[00130] In some embodiments, the pharmaceutical composition comprises a second diluent in about 95% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 90% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 85% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 80% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 70% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 65% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 55% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 45% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 30% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 20% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 5% by weight of the dosage form.

[00131] In some embodiments, the diluent is selected from calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose. In some embodiments, the diluent is lactose monohydrate. In some embodiments, the diluent is microcrystalline cellulose. In some embodiments, the diluent is calcium carbonate. In some embodiments, the diluent is calcium phosphate. In some embodiments, the diluent is starch. In some embodiments, the diluent is pregelatinized starch. In some embodiments, the diluent is sodium carbonate. In some embodiments, the diluent is mannitol.

[00132] In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 9% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 2% by weight of the dosage form.

[00133] In some embodiments, the pharmaceutical composition comprises a binder in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 9% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 2% by weight of the dosage form. In

some embodiments, the pharmaceutical composition comprises a binder in about 1% by weight of the dosage form.

[00134] In some embodiments, the binder is selected from starches (corn starch and potato starch), gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC). In some embodiments, the binder is hydroxypropyl cellulose (HPC). In some embodiments, the binder is starch. In some embodiments, the binder is gelatin. In some embodiments, the binder is polyvinylpyrrolidone (PVP). In some embodiments, the binder is hydroxypropyl methyl cellulose (HPMC).

[00135] In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 4.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 4.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 3.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 3.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 2.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 2.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 1.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 1% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 0.8% by weight of the dosage form.

[00136] In some embodiments, the pharmaceutical composition comprises a surfactant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 4.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 4.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 3.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 3.0% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 2.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 2.0% by weight of the dosage form. In some embodiments,

the pharmaceutical composition comprises a surfactant in about 1.5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 1% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.75% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.25% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.1% by weight of the dosage form.

[00137] In some embodiments, the surfactant is selected from sodium lauryl sulfate, cetrimide, benzalkonium chloride, cetylpyridinium chloride, alkylsulphates, alkylethoxylate sulphates, soaps, carboxylate ions, sulfate ions, sulfonate ions, polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glocol, glycerol esters, sorbitan derivatives, polyethylene glycol (such as PEG-40, PEG-50, or PEG-55) and esters of fatty alcohols. In some embodiments, the surfactant is sodium lauryl sulfate.

[00138] In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 9% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 1.5% by weight of the dosage form.

[00139] In some embodiments, the pharmaceutical composition comprises a disintegrant in about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 9% by weight of the dosage form. In some

embodiments, the pharmaceutical composition comprises a disintegrant in about 8% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 7% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% by weight of the dosage form.

[00140] In some embodiments, the disintegrant is selected from starch, alginic acid, ac-di-sol, croscarmellose sodium, sodium starch glycolate, and crospovidone. In some embodiments the disintegrant is croscarmellose sodium. In some embodiments the disintegrant is sodium starch glycolate. In some embodiments the disintegrant is crospovidone.

[00141] In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% to about 2% by weight of the dosage form.

[00142] In some embodiments, the pharmaceutical composition comprises a glidant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 1% by weight of the dosage form.

[00143] In some embodiments the glidant is colloidal silicon dioxide.

[00144] In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% to about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in

about 1% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% to about 2% by weight of the dosage form.

[00145] In some embodiments, the pharmaceutical composition comprises a lubricant in about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 4% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 1% by weight of the dosage form.

[00146] In some embodiments the lubricant is selected from talc, stearic acid, magnesium stearate and sodium stearyl fumarate. In some embodiments, the lubricant is talc. In some embodiments, the lubricant is stearic acid. In some embodiments, the lubricant is magnesium stearate. In some embodiments, the lubricant is sodium stearyl fumarate.

[00147] In some embodiments, the pharmaceutical composition comprises a granulating agent. In some embodiments, the granulating agent is purified water.

[00148] In some embodiments, the pharmaceutical composition comprises a first diluent in about 10% to about 60% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 10% to about 40% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in about 1% to about 10% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 0.5% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 0.5% to about 5%.

[00149] In some embodiments, the pharmaceutical composition comprises a first diluent in about 35% to about 50% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in about 15% to about 35% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in about 1% to about 5% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in about 0.5% to about 2% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a

disintegrant in about 2% to about 6% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in about 0.5% to about 3% by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in about 0.5% to about 3% by weight of the dosage form.

Amounts

[00150] In some embodiments, the pharmaceutical composition comprises between about 50 mg and about 200 mg. In some embodiments, the pharmaceutical composition comprises about 50 mg. In some embodiments, the pharmaceutical composition comprises about 200 mg. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 500 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 450 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 400 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 350 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 300 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 250 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 200 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 175 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 150 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 125 mg of the crystalline composition comprising Compound 1 (e.g.,comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 100 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 90 mg of the crystalline comprising

Compound 1 (e.g., composition comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 80 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 70 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 60 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 50 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 40 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 30 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 20 mg of the crystalline composition comprising Compound 1 (e.g.,comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 10 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 9 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 8 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 7 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 6 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 5 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 4 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 3 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments,

the pharmaceutical composition comprises between about 1 mg and about 2 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[00151] In some embodiments, the pharmaceutical composition comprises between about 500 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 450 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 400 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 350 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 300 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I. In some embodiments, the pharmaceutical composition comprises between about 250 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 200 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 150 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 100 mg of the crystalline comprising Compound 1 (e.g., composition comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 90 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 80 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 70 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 60 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 50 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 40 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 30 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some

embodiments, the pharmaceutical composition comprises between about 20 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 10 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 5 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I). In some embodiments, the pharmaceutical composition comprises between about 1 mg of the crystalline composition comprising Compound 1 (e.g., comprising Formula I).

[00152] In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises between about 50 mg and about 200 mg of Compound 1. In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises about 50 of Compound 1. In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises about 100 of Compound 1. In some embodiments, the pharmaceutical composition (e.g., crystalline composition) comprising Compound 1 comprises about 200 of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 500 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 450 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 400 mg Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 350 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 300 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 250 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 200 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 175 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 150 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 125 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 100 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 90 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 80 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and

about 70 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 60 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 50 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 40 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 30 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 20 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 10 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 9 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 8 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 7 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 6 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 5 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 4 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 3 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 2 mg of Compound 1.

[00153] In some embodiments, the pharmaceutical composition comprises about 500 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 450 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 400 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 350 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 300 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 250 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 200 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 150 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 90 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 80 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 70 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 60 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 50

mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 40 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 30 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 20 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 10 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 5 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 1 mg Compound 1.

[00154] In some embodiments, the pharmaceutical composition comprises Compound I in about 25 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in about 10 % to about 50 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in about 10 % to about 15 %, about 10 % to about 20 %, about 10 % to about 25 %, about 10 % to about 30 %, about 10 % to about 35 %, about 10 % to about 40 %, about 10 % to about 45 %, about 10 % to about 50 %, about 15 % to about 20 %, about 15 % to about 25 %, about 15 % to about 30 %, about 15 % to about 35 %, about 15 % to about 40 %, about 15 % to about 45 %, about 15 % to about 50 %, about 20 % to about 25 %, about 20 % to about 30 %, about 20 % to about 35 %, about 20 % to about 40 %, about 20 % to about 45 %, about 20 % to about 50 %, about 25 % to about 30 %, about 25 % to about 35 %, about 25 % to about 40 %, about 25 % to about 45 %, about 25 % to about 50 %, about 30 % to about 35 %, about 30 % to about 40 %, about 30 % to about 45 %, about 30 % to about 50 %, about 35 % to about 40 %, about 35 % to about 45 %, about 35 % to about 50 %, about 40 % to about 45 %, about 40 % to about 50 %, or about 45 % to about 50 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, or about 50 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in at least about 10 %, about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, or about 45 % w/w. In some embodiments, the pharmaceutical composition comprises Compound I in at most about 15 %, about 20 %, about 25 %, about 30 %, about 35 %, about 40 %, about 45 %, or about 50 % w/w.

[00155] In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 500 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 450 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 400 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to

about 350 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 300 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 250 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 200 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 150 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 100 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 90 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 80 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 70 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 60 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 50 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 40 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 30 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is between about 10 mg to about 20 mg.

[00156] In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 300 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 200 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 20 mg. In some

embodiments, the pharmaceutical composition comprises a diluent in an amount that is about 10 mg.

[00157] In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 300 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 200 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is about 10 mg.

[00158] In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 300 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 200 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is about 10 mg.

[00159] In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 100 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 90 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 80 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 70 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 60 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and about 5 mg.

[00160] In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises

a binder in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is about 1 mg.

[00161] In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 9 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 8 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 7 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 6 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 5 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 4 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 3 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 2 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg and about 1.5 mg.

[00162] In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is

about 20 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1.75 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1.5 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1.25 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is about 1 mg.

[00163] In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 100 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 90 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 80 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 70 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 60 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 50 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 40 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 30 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 20 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 10 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 9 mg. In some embodiments,

the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 8 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 7 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 6 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 5 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 4 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 3 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 2 mg.

[00164] In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 100 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 90 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 80 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 70 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 60 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 2 mg. In

some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is about 1 mg.

[00165] In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 45 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 35 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 25 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 15 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 5 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg and about 2 mg.

[00166] In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 4 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 3 mg. In some

embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is about 1 mg.

[00167] In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 50 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 45 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 40 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 35 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 30 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 25 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 20 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 15 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 10 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 5 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg and about 2 mg.

[00168] In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 50 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 40 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 30 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 20 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 10 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 9 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 8 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 7 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 6 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 5 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 4 mg. In some

embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 3 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 2 mg. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is about 1 mg.

[00169] In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is between about 1 mg to about 200 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is between about 1 mg to about 200 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg to about 50 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg to about 50 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg to about 50 mg by weight of the dosage form.

[00170] In some embodiments, the pharmaceutical composition comprises a first diluent in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a second diluent in an amount that is between about 1 mg to about 100 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a binder in an amount that is between about 1 mg and 20 mg. In some embodiments, the pharmaceutical composition comprises a surfactant in an amount that is between about 1 mg to about 10 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a disintegrant in an amount that is between about 1 mg to about 20 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a glidant in an amount that is between about 1 mg to about 20 mg by weight of the dosage form. In some embodiments, the pharmaceutical composition comprises a lubricant in an amount that is between about 1 mg to about 20 mg by weight of the dosage form.

Particle size

[00171] In some embodiments, the pharmaceutical composition (e.g., comprising the crystalline composition comprising Compound 1 (e.g., comprising Formula I)) is in the form

of microparticles. In some embodiments, microparticles of the crystalline composition comprising Compound 1 (e.g., comprising Formula I) have an average size from about 1 μm to about 100 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 90 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 80 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 70 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 60 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 50 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 40 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 30 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 20 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 10 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm to about 5 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 100 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 90 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 80 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 70 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 60 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 50 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 40 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 30 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 20 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 10 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 9 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 8 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 7 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 6 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 5 μm. In some embodiments,

microparticles of the crystalline composition have an average size from about 4 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 3 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 2 μm. In some embodiments, microparticles of the crystalline composition have an average size from about 1 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 100 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 90 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 80 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 70 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 60 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 50 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 40 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 30 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 20 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 10 μm. In some embodiments, microparticles of the crystalline composition have an average size less than about 5 μm.

[00172] In some embodiments, the pharmaceutical composition comprises the crystalline composition comprising Compound 1 (e.g., comprising Formula I), wherein the crystalline composition has a D90 from about 1 μm to about 50 μm. In some embodiments, the crystalline composition has a D90 from about 1 μm to about 20 μm, from about 2 μm to about 19 μm, from about 3 μm to about 18 μm, from about 4 μm to about 17 μm, from about 5 μm to about 16 μm, from about 6 μm to about 15 μm, from about 7 μm to about 14 μm, from about 8 μm to about 13 μm, from about 9 μm to about 13 μm, or from about 8 μm to about 12 μm. In some embodiments, the pharmaceutical composition comprises the crystalline composition comprising Compound 1 (e.g., comprising Formula I), wherein the crystalline composition has a D90 of more than about 1 μm, more than about 2 μm, more than about 3 μm, more than about 4 μ, more than about 5 μm, more than about 6 μm, more than about 7 μm, more than about 8 μm, more than about 9 μm, more than about 10 μm, more than about 11 μm, more than about 12 μm, more than about 13 μm, more than about 14 μm more than about 15 μm more than about 16 μm, more than about 17 μm, more than about 18 μm, or more than about 19 μm. In some embodiments, the crystalline composition has a

D90 of less than about 20 μm, less than about 19 μm, less than about 18 μm, less than about 17 μm, less than about 16 μm, less than about 15 μm, less than about 14 μm, less than about 13 μm, less than about 12 μm, or less than about 11 μm.

[00173] In some embodiments, the pharmaceutical composition comprising Compound 1 is in the form of microparticles. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 100 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 90 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 80 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 70 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 60 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 50 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 40 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 30 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 20 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm to about 5 μm. In some embodiments, microparticles of Compound 1 have an average size from about 100 μm. In some embodiments, microparticles of Compound 1 have an average size from about 90 μm. In some embodiments, microparticles of Compound 1 have an average size from about 80 μm. In some embodiments, microparticles of Compound 1 have an average size from about 70 μm. In some embodiments, microparticles of Compound 1 have an average size from about 60 μm. In some embodiments, microparticles of Compound 1 have an average size from about 50 μm. In some embodiments, microparticles of Compound 1 have an average size from about 40 μm. In some embodiments, microparticles of Compound 1 have an average size from about 30 μm. In some embodiments, microparticles of Compound 1 have an average size from about 20 μm. In some embodiments, microparticles of Compound 1 have an average size from about 10 μm. In some embodiments, microparticles of Compound 1 have an average size from about 9 μm. In some embodiments, microparticles of Compound 1 have an average size from about 8 μm. In some embodiments, microparticles of Compound 1 have an average size from about 7 μm. In some embodiments, microparticles of Compound 1 have an average size from about 6 μm. In some embodiments, microparticles of Compound 1 have an average size from about 5 μm. In some embodiments, microparticles of Compound 1 have an

average size from about 4 μm. In some embodiments, microparticles of Compound 1 have an average size from about 3 μm. In some embodiments, microparticles of Compound 1 have an average size from about 2 μm. In some embodiments, microparticles of Compound 1 have an average size from about 1 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 100 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 90 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 80 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 70 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 60 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 50 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 40 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 30 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 20 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 10 μm. In some embodiments, microparticles of Compound 1 have an average size less than about 5 μm.

[00174] In some embodiments, the pharmaceutical composition comprises Compound 1, wherein Compound 1 has a D90 from about 1 μm to about 50 μm. In some embodiments, Compound 1 has a D90 from about 1 μm to about 20 μm, from about 2 μm to about 19 μm, from about 3 μm to about 18 μm, from about 4 μm to about 17 μm, from about 5 μm to about 16 μm, from about 6 μm to about 15 μm, from about 7 μm to about 14 μm, from about 8 μm to about 13 μm, from about 9 μm to about 13 μm, or from about 8 μm to about 12 μm. In some embodiments, the pharmaceutical composition comprises Compound 1 , wherein Compound 1 has a D90 of more than about 1 μm, more than about 2 μm, more than about 3 μm, more than about 4 μ, more than about 5 μm, more than about 6 μm, more than about 7 μm, more than about 8 μm, more than about 9 μm, more than about 10 μm, more than about 11 μm, more than about 12 μm, more than about 13 μm, more than about 14 μm more than about 15 μm more than about 16 μm, more than about 17 μm, more than about 18 μm, or more than about 19 μm. In some embodiments, Compound 1 has a D90 of less than about 20 μm, less than about 19 μm, less than about 18 μm, less than about 17 μm, less than about 16 μm, less than about 15 μm, less than about 14 μm, less than about 13 μm, less than about 12 μm, or less than about 11 μm.

Methods of Preparing the Crystalline Composition Comprising Compound I (e.g., Comprising Formula I)

[00175] Isolation and purification of the chemical entities and intermediates described herein can be performed, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples below. However, other equivalent separation or isolation procedures can also be used. Prior to crystallization, Compound 1 may be isolated in about 50% chemical purity, 55% chemical purity, 60% chemical purity, 65% chemical purity, 70% chemical purity, 75% chemical purity, 80% chemical purity, 90% chemical purity, 91% chemical purity, 92% purity, 93% chemical purity, 94% chemical purity, 95% chemical purity, 96% chemical purity, 97% chemical purity, 98% chemical purity, 99% chemical purity, about 98% chemical purity, or about 100% chemical purity.

[00176] In some embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) disclosed herein are obtained by crystallizing Compound 1 with a chemical purity of less than about 98%, less than about 97%, less than about 96%, less than about 95%, less than about 94%, less than about 93%, less than about 92%, less than about 91%, less than about 90%, less than about 89%, less than about 88%, less than about 87%, less than about 86%, less than about 85%, less than about 84%, less than about 83%, less than about 82%, less than about 81%, less than about 80%, less than about 78%, less than about 76%, less than about 74%, less than about 72%, or less than about 70%. In some embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is obtained by crystallizing Compound 1 with a chemical purity in the range of about 70% to about 99%, 80% to about 96%, about 85% to about 96%, about 90% to about 96%, about 80% to 98%, about 85% to about 98%, about 90% to about 98%, about 92% to about 98%, about 94% to 98%, or about 96% to about 98%.

Preparation of Crystalline Form I

[00177] In some aspects, the present disclosure provides a method of preparing a crystalline composition comprising Compound I (e.g., comprising Formula I), wherein the method comprises:

(a) dissolving 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) and an acid (e.g., oxalic acid) in a solvent;

(b) heating the solution or slurry from step (a); and

(c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound I (e.g., comprising Formula I).

[00178] In some embodiments, the solvent in step (a) comprises acetone, heptane, water, 2-butanol, ethyl acetate, 2-propanol, methyl tert-butyl ether, ethanol, methyl ethyl ketone, 1-pentanol, or a combination thereof. In some embodiments, the solvent in step (a) is heptane. In some embodiments, the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone. In some embodiments, the solvent in step (a) is a mixture of heptane and methyl ethyl ketone.

[00179] In some embodiments, step (b) is heated at about 50 °C. In some embodiments, step (b) is heated to at least about 50 °C.

[00180] In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between about 20 mg/mL and about 300 mg/mL. In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between about 40 mg/mL and about 250 mg/mL. In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between about 100 mg/mL and about 200 mg/mL. In some embodiments, the concentration of the solution comprising Compound 1 obtained in step (a) is between 125 mg/mL and about 175 mg/mL.

[00181] In various embodiments, the method of preparing the crystalline composition comprising Compound I (e.g., comprising Formula I) involves recrystallization of Compound 1 from a binary, tertiary, or greater solvent system, collectively understood as a multi-solvent system. In some embodiments, the method of preparing the crystalline composition comprising Compound I (e.g., comprising Formula I) involves crystallization from a mono- or multi-solvent system, where the crystallization involves dissolving Compound 1 in the mono- or multi-solvent system at a temperature above ambient temperature. In some embodiments, the dissolving of Compound 1 in the mono- or multi-solvent system is performed at a temperature of about 0-90 °C, 5-90 °C, 10-90 °C, 15-90 °C, 20-90 °C, 25-90 °C, 30-90 °C, 35-90 °C, 40-90 °C, 45-90 °C, 50-90 °C, 55-90 °C, 60-90 °C, 65-90 °C, 70-90 °C, 75-90 °C, 80-90 °C, 85-90 °C, 0-80 °C, 5-80 °C, 10-80 °C, 20-80 °C, 30-80 °C, 40-80 °C, 50-80 °C, 60-80 °C, 70-80 °C, 0-70 °C, 5-70 °C, 10-70 °C, 15-70 °C, 20-70 °C, 30-70 °C, 40-70 °C, 50-70 °C, 60-70 °C, 0-60 °C, 10-60 °C, 20-60 °C, 30-60 °C, 40-60 °C, or 50-60 °C.

[00182] In various embodiments, the crystallization further involves actively heating the solution containing the dissolved Compound 1, for example to a temperature of about 40-100

°C, 40-90 °C, 40-80 °C, 40-70 °C, 40-60 °C, 40-50 °C, 50-100 °C, 50-90 °C, 50-80 °C, 50-70 °C, 50-60 °C, 60-100 °C, 60-90 °C, 60-80 °C, 60-70 °C, 70-100 °C, 70-90 °C, 70-80 °C, 80-100 °C, or 80-90 °C. In various embodiments, the solution containing the dissolved Compound 1 is maintained at the heated temperature for a period of time, for example for about 30 min, about 1 h, about 2 h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h, about 11 h, about 12 h, about 13 h, about 14 h, about 15 h, about 16 h, about 17 h, about 18 h, about 19 h, about 20 h, about 21 h, about 22 h, about 23 h, about 24 h or more.

[00183] In various embodiments, the crystallization further involves actively cooling the heated solution containing the dissolved Compound 1, for example to a temperature of about 0-40 °C, 0-30 °C, 0-20 °C, 0-10 °C, 10-40 °C, 10-30 °C, 10-20 °C, 20-40 °C, 20-30 °C, 20-10 °C, or 30 °C-40 °C. In some embodiments, the crystallization further involves actively cooling the heated solution containing the dissolved Compound 1 to a temperature of about 20-30 °C. In various embodiments, the solution containing the dissolved Compound 1 is further maintained at this lower temperature for a time period, for example for about 30 min, about 1 h, about 2 h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h, about 11 h, about 12 h, about 13 h, about 14 h, about 15 h, about 16 h, about 17 h, about 18 h, about 19 h, about 20 h, about 21 h, about 22 h, about 23 h, about 24 h or more.

[00184] In various embodiments, the steps of active heating followed by active cooling are repeated multiple times, for example at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 times. In some embodiments, the steps of active heating followed by active cooling are repeated 2, 3, 4, 5, 6, 7, 8, 9, or 10 times.

[00185] In various embodiments, the crystallization further involves filtering the solution containing the obtained crystals of the crystalline composition comprising Compound I (e.g., comprising Formula I). In some embodiments, the crystallization optionally involves washing the obtained crystals by a solvent, for example by the recrystallization solvent one or more times. In some embodiments, the crystallization optionally involves drying the obtained crystals, for example under vacuum.

[00186] In some embodiments, the chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than 60%, 70%, 80%, 90%, 95%, or 99%. In some embodiments, the chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than about 90%. In some embodiments, the chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than about 95%. In some embodiments, the chemical purity of the

crystalline composition comprising Compound I (e.g., comprising Formula I) is greater than about 99%. The chemical purity of the crystalline composition comprising Compound I (e.g., comprising Formula I) may be measured by any available analytical technique, for example by HPLC analysis.

[00187] In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is dry. In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is non-solvated. In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is non-hydrated. In various embodiments, the crystalline composition comprising Compound I (e.g., comprising Formula I) is anhydrous.

Methods of Treatment

[00188] In another aspect, the present disclosure provides a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound 1 as described herein, or a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the subject has congenital adrenal hyperplasia (CAH).

[00189] In another aspect, the present disclosure provides a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or a pharmaceutical composition comprising a crystalline composition comprising Formula I as described herein. In some embodiments, the CAH is classic CAH. In some embodiments, the CAH is non-classical CAH.

[00190] In another aspect, the present disclosure provides a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the hyperandrongic symptoms are selected from the group consisting of acne, hirsutism, and alopecia.

[00191] In another aspect, the present disclosure provides a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or a pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein.

[00192] In another aspect, the present disclosure provides a method of improving metabolic symptoms in a subject in need thereof, comprising administering to the subject a a composition comprising Compound I, or crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the metabolic symptoms are selected from the group consisting of body weight, BMI, fat mass, waist circumference, blood pressure and glycemic control.

[00193] In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein.

[00194] In another aspect, the present disclosure provides a method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein.

[00195] In another aspect, the present disclosure provides a method of treating endometriosis or improving the symptoms of endometriosis in a subject in need thereof, comprising administering to the subject a composition comprising Compound I, or a crystalline composition comprising Compound I (e.g., comprising Formula I) as described herein, or the pharmaceutical composition comprising the crystalline composition comprising Formula I as described herein. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition improves the symptom of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the

pharmaceutical composition reduces the symptoms of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition prevents the symptom of pain experienced by the subject. In some embodiments, the administration of the crystalline composition or the pharmaceutical composition eliminates the symptom of pain experienced by the subject.

[00196] In some embodiments, the methods described herein result in the reduction of a hormone level. Such hormones include deoxycorticosterone, 11-deoxycortisol, Cortisol, corticosterone, aldosterone, pregnenolone, hydroxy pregnenolone, progesterone, 17a-hydroxy progesterone (17-OHP), dehydroepiandrosterone, androstenediol, androstenedione, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein result in the reduction of 17a-hydroxy progesterone (17-OHP). In some embodiments, the methods described herein result in the reduction of adrenocorticotropic hormone (ACTH), also known as corticotropin.

[00197] In various embodiments of the methods as described herein, a composition comprising Compound I, or the crystalline composition or the pharmaceutical composition (e.g., comprising Compound 1) is administered at a dose from about 5 mg/day to about 1000 mg/day. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fed state. In some embodiments, the crystalline composition or the pharmaceutical composition is administered in a fasted state. In some embodiments, the crystalline composition or the pharmaceutical composition is administered at least once per day.

[00198] In some embodiments of the methods described herein, the composition, or the crystalline composition or the pharmaceutical composition is administered at bedtime. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical composition described herein less than about 4 hours before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical composition described herein less than about 3 hours before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical composition described herein less than about 2 hours before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical compositions described herein less than about 1 hour before sleep. In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical compositions described herein less than about 30 mins before sleep.

[00199] In some embodiments, the methods described herein include administration of the crystalline composition (e.g., comprising Compound 1) or the pharmaceutical compositions (e.g., comprising Compound 1) described herein at or before the expected circadian release of adrenocorticotropic hormone (ACTH). In some embodiments, the methods described herein include administration of the crystalline composition or the pharmaceutical compositions described herein about 3-4 hours before the expected circadian release of adrenocorticotropic hormone (ACTH).

[00200] In various embodiments of the methods as described herein, the method further comprises administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen agent. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone. In some embodiments, the additional therapeutic agent is another CRF1antagonist.

[00201] In various embodiments of the methods as described herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, or the pharmaceutical composition comprising the crystalline composition as described herein. In some embodiments, the additional therapy is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the crystalline composition as described herein, or the pharmaceutical composition comprising the crystalline composition as described herein.

[00202] In various embodiments of the methods, the subject is from about 9 years of age to about 18 years of age. In some embodiments, the subject is from about 8 years of age to about 55 years of age.

[00203] In some aspects, described herein are crystalline compositions comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3- fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propynyl)-1,3-thiazol- 2-amine ("crinecerfont"). In some embodiments, crinecerfont is a salt (e.g., hydrochloric acid salt, p-toluenesulfonic acid salt, etc.). Pharmaceutically acceptable acid addition salts of crinecerfont may be formed by combining a compound having a basic moiety with inorganic acids and organic acids. Inorganic acids which may be used to prepare salts of crinecerfont include, for example,

hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids which may be used to prepare salts of crinecerfont include, for example, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and the like. Pharmaceutically acceptable base addition salts of crinecerfont may be formed by combining a compound having an acidic moiety with inorganic and organic bases. Inorganic bases which may be used to prepare salts of crinecerfont include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, manganese, aluminum hydroxides, carbonates, bicarbonates, phosphates, and the like. In some embodiments, the inorganic base salt is ammonium, potassium, sodium, calcium, and magnesium hydroxides, carbonates, bicarbonates, or phosphates. Organic bases from which may be used to prepare salts of crinecerfont include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Generally, such salts of crinecerfont may be prepared by reacting the free acid or base forms of these compounds with at least a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN). In some embodiments, they crystalline composition comprises crinecerfont and oxalic acid.

[00204] In some embodiments, the crystalline composition comprising crinecerfont comprises crinecerfont and an acid in a ratio of crinecerfont to acid of about 2:1, about 1:1, or about 1:2.

[00205] In some embodiments, the composition comprising crinecerfont is in a capsule (e.g., an immediate-release capsule or a capsule for opening (e.g., comprising crinecerfont granules).

[00206] In some aspects, disclosed herein are methods of administering a composition (e.g., crystalline composition) comprising crinecerfont. In some embodiments, the method further comprises administering an additional therapeutic. In some embodiments, the additional therapeutic. In some embodiments, the additional therapeutic comprises hydrocortisone. In some embodiments, the hydrocortisone is an immediate-release hydrocortisone. In some embodiments, the hydrocortisone is in a capsule (e.g., a capsule for opening (e.g., hydrocortisone granules in a capsule)). In some embodiments, the hydrocortisone is an modified-release hydrocortisone. In some embodiments, the hydrocortisone is in a hard-capsule (e.g., a modified-release hard capsule).

ADDITIONAL EMBODIMENTS

[00207] The following embodiments are given for the purpose of illustrating various embodiments of the disclosure and are not meant to limit the present disclosure or any aspect thereof (e.g., element) in any fashion. The following embodiments may include additional elements disclosed herein. Changes therein and other uses which are encompassed within the spirit of the disclosure as defined by the scope of the claims will occur to those skilled in the art.

1. A pharmaceutical formulation, comprising:

(a) about 10 mg to about 300 mg of 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-α) pyrimidine (Compound 1), or a pharmaceutically acceptable salt or solvate thereof;

(b) a first diluent in about 40% to about 45% by weight, wherein the first diluent comprises lactose monohydrate;

(c) a second diluent in about 25% by weight, wherein the second diluent comprises microcrystalline cellulose;

(d) about 1% to about 6% by weight of hydroxypropyl cellulose;

(e) about 0.5% to about 5% by weight of sodium lauryl sulfate; and

(f) about 4% by weight of croscarmellose sodium.

2. The pharmaceutical formulation of embodiment 1, further comprising a glidant, wherein the glidant comprises colloidal silicon dioxide.

3. The pharmaceutical formulation of embodiment 1, further comprising a lubricant, wherein the lubricant comprises magnesium stearate.

4. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is about 1% by weight of the pharmaceutical formulation.

5. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is in an amount that is about 2 mg.

6. The pharmaceutical formulation of embodiment 1, wherein Compound 1 or a pharmaceutically acceptable salt thereof is in an amount that is about 50 mg.

7. The pharmaceutical formulation of embodiment 1, wherein the lactose monohydrate is about 40.25% by weight of the pharmaceutical formulation.

8. The pharmaceutical formulation of embodiment 1, wherein the lactose monohydrate is in an amount that is about 80.50 mg.

9. The pharmaceutical formulation of embodiment 1, wherein the microcrystalline cellulose is in an amount that is about 50 mg.

10. The pharmaceutical formulation of embodiment 1, wherein the hydroxypropyl cellulose is about 3% by weight of the pharmaceutical formulation.

11. The pharmaceutical formulation of embodiment 1, wherein the hydroxypropyl cellulose is in an amount that is about 6 mg.

12. The pharmaceutical formulation of embodiment 1, wherein the sodium lauryl sulfate is about 0.75% by weight of the pharmaceutical formulation.

13. The pharmaceutical formulation of embodiment 1, wherein the sodium lauryl sulfate is in an amount that is about 1.50 mg.

14. The pharmaceutical formulation of embodiment 1, wherein the croscarmellose sodium is in an amount that is about 8 mg.

15. The pharmaceutical formulation of embodiment 2, wherein the colloidal silicon dioxide is about 1% by weight of the pharmaceutical formulation.

16. The pharmaceutical formulation of embodiment 2, wherein the colloidal silicon dioxide is in an amount that is about 2 mg.

17. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is about 1% by weight of the pharmaceutical formulation.

18. The pharmaceutical formulation of embodiment 3, wherein the magnesium stearate is in an amount that is about 2 mg.

19. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is in a tablet form.

20. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is in a granule form.

21. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is in a capsule.

22. The pharmaceutical formulation of embodiment 1, wherein the pharmaceutical formulation is packaged in a sachet.

EXAMPLES

[00208] The following examples serve to further describe the manner of using the present disclosure. These examples are presented for illustrative purpose and should not serve to limit the true scope of the present disclosure.

[00209] In carrying out the procedures of the methods described herein, it is of course to be understood that references to particular buffers, media, reagents, cells, culture conditions, and the like are not intended to be limiting, but are to be read so as to include all related materials

that one of ordinary skill in the art would recognize as being of interest or value in the particular context in which that discussion is presented. For example, it is often possible to substitute on buffer system or culture medium for another and still achieve similar, if not identical, results. Those of skill in the art will have sufficient knowledge of such systems and methodologies so as to able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

Example 1 – Preparation and Characterization of the Crystalline Composition Comprising Compound I (e.g., comprising Formula I)

Preparation of the Crystalline Composition Comprising Compound I (e.g., comprising Formula I)

[00210] A mixture of 185.0 mg (0.441 mmol) of 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (**Compound 1**), 45.0 mg (0.500 mmol) of oxalic acid, and 2.5 mL of diisopropyl ether was agitated. After one hour, an additional 1 mL of diisopropyl ether was added. After stirring overnight, the mixture was vacuum filtered and the resulting solid was dried to afford 170 mg (76%) of the crystalline composition comprising Compound I (e.g., comprising Formula I) as solid.

X-Ray Powder Diffraction

[00211] X-ray powder diffraction (XPRD) patterns were obtained on a Rigaku Smart-Lab X-ray diffraction system. A CuK source (=0.71073 Å) operating minimally at 40 kV and 44 mA scans each sample between 2 and 40 degrees 2θ. The step size is 0.02° 2θ.

[00212] The XRPD pattern obtained for the crystalline composition comprising Compound I (e.g., comprising Formula I) is summarized in Table 1 below and shown in **FIG. 1**.

Table 1 – XRPD Data of the Crystalline Composition Comprising Compound I (e.g., **comprising Formula I)**

Peak #	Angle (° 2-θ)	Intensity (%)	Peak #	Angle (° 2-θ)	Intensity (%)
1	5.44	31	**26**	26.58	4
2	8.82	12	**27**	26.80	14
3	10.84	100	**28**	26.94	8
4	11.70	12	**29**	27.62	3
5	14.60	8	**30**	28.00	13

Table 1 – XRPD Data of the Crystalline Composition Comprising Compound I (e.g., **comprising Formula I)**					
6	15.56	6	**31**	28.86	14
7	15.96	52	**32**	29.54	3
8	16.28	5	**33**	31.26	3
9	16.70	10	**34**	31.66	5
10	17.66	4	**35**	31.88	4
11	18.44	5	**36**	32.16	3
12	18.82	6	**37**	32.48	2
13	19.18	8	**38**	32.86	5
14	19.60	2	**39**	33.46	2
15	20.02	11	**40**	34.36	2
16	20.50	11	**41**	35.02	3
17	20.78	20	**42**	35.44	1
18	21.72	7	**43**	35.98	2
19	22.12	2	**44**	36.72	4
20	22.74	18	**45**	37.04	3
21	23.04	16	**46**	37.80	5
22	23.44	31	**47**	38.28	2
23	24.80	48	**48**	38.90	2
24	25.52	6	**49**	39.20	2
25	25.92	9			

Differential Scanning Calorimetry (DSC)

[00213] Differential scanning calorimetry analysis was carried out on a TA Instruments Q2500 Discovery Series instrument. The instrument temperature calibration was performed using indium. The DSC cell was kept under a nitrogen purge of about 50 mL per minute during each analysis. The sample was placed in a standard, crimpled, aluminum pan and was heated from approximately 25 °C to 350 °C at a rate of 10 °C per minute. The DSC trace of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 2**.

Thermogravimetric Analysis (TGA)

[00214] Thermogravimetry analyses were carried out using a TA Instruments Discovery TGA 5500 instrument that was cooled using a TA Instruments Refrigerated Cooling System (RCS) 90 chiller. The instrument balance was calibrated using class M weights and temperature calibration was performed by measurement of the Curie point of Alumel®. Sample was loaded onto a platinum sample pan and the pan was loaded into the TG instrument. The pan was heated from ambient temperature to 350 °C at a rate of 10 °C per minute. The instrument was controlled using TA Trios software. The TGA trace of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 3**.

Dynamic Vapor Sorption (DVS)

[00215] The DVS analysis was carried out on a TA Instruments Q5000 sorption analyzer. The instrument was calibrated with standard weights and a sodium bromide standard for humidity. For each analysis, a portion of the sample was weighed into a metal-coated, quartz pan. Each sample was analyzed at 25 °C with a maximum equilibration time of 60 minutes in 10% relative humidity (RH) steps from 5 to 95% RH (adsorption cycle) and from 95 to 5% RH (desorption cycle). Data collection was performed using Advantage for Q Series version 5.5.23. The percent weight change values were calculated using Microsoft Excel®. The DVS trace of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 4**.

Infrared (IR)

[00216] The IR spectrum was obtained using a Nicolet iS50 Model 60825 Fourier-transform (FT) IR spectrophotometer equipped with a deuterated triglycine sulfate (DTGS) detector, a potassium bromide (KBr) beamsplitter, and an electronically temperature controlled (ETC) Ever-Glo® IR source. The instrument was configured with a SMART iTR diamond attenuated total reflectance (ATR) sampling accessory. The single beam scan of the background (air) and sample were collected with 128 signal-averaged scans at a resolution of 2 cm-1 over the spectral range 400-4000 cm-1. The wavelength calibration was verified using a certified polystyrene standard. Data collection and processing was performed using Omnic 9.2 software. The IR spectrum of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 5**.

Proton Nuclear Magnetic Resonance (^{1}H NMR)

[00217] The 1H NMR spectrum was acquired on a Bruker Avance 400 MHz spectrometer using TopSpin v3.2 software. The sample was dissolved in CD_3OD and the resulting solution was transferred into a 5-mm NMR tube for subsequent data acquisition. Data collection parameters are shown in Table 14. The spectrum was processed using the program MNova and referenced to the chemical shift of the residual protons in CD_3OD (3.31 ppm). The ^{1}H NMR spectrum of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 6**.

Raman

[00218] The Raman spectrum was acquired utilizing a Thermo Scientific model iS50 Fourier-transform (FT) IR spectrophotometer equipped with a Raman accessory. The system is equipped with an indium gallium arsenide (InGaAs) detector, a calcium fluoride (CaF2) beamsplitter, and a 2.5 W laser operating at 1064 nm. The module was configured with a 180° reflective sampling accessory. A sample was prepared by loading particles onto a glass slide. Each FT-Raman spectrum was collected using 0.50 W laser power with 256 signal-averaged scans at a resolution of 4 cm-1 over the spectral range 100-3700 cm-1. The wavelength calibration was verified using a polystyrene. Data acquisition and processing were performed using Omnic 9.7 software. The Raman spectrum of the crystalline composition comprising Compound I (e.g., comprising Formula I) is shown in **FIG. 7**.

Example 2 – Formulation Comprising Compound 1

General Manufacturing Procedure

[00219] The relevant excipients were manually sieved and then dry mixed. A binder solution was added and the mixture subjected to wet granulation. The granules were then wet milled and dried. The resulting granules were dry milled and added to other relevant common granules and excipients. The mixture was then compressed into tablets to a target tablet weight.

[00220] A granulation was developed with a minimum amount and number of excipients. The granulation comprised of Compound 1 ("Tildacerfont") with a surfactant and a binder and, in some cases, a super-disintegrant. After granulation was successful, other excipients were added to enable compression. These excipients included a compression aid, a lubricant, an anti-tacking agent, and a super-disintegrant.

[00221] Table 1 below summarizes formulations comprising Tildacerfont in both tablet and granules form.

Table 2 – Formulation Comprising Tildacerfont

Material Description	Function	%w/w	mg/Tablet	Granules
			50 mg strength	50 mg strength
Intragranular				
Tildacerfont (SPN001)	Active ingredient	25.00	50.00	50.00
Lactose Monohydrate, USP/NF, Ph. Eur., JP. (Pharmatose 200M EU)	Diluent	40.25	80.50	80.50
Hydroxypropylcellulose USP/NF, Ph. Eur., JP (Klucel EXF)	Binder	3.00	6.00	6.00
Sodium Lauryl Sulfate, NF/ Ph. Eur./JP (Kolliphor SLS fine)	Surfactant	0.75	1.50	1.50
Microcrystalline Cellulose, NF, Ph.Eur., JP (Avicel PH101)	Diluent	20.00	40.00	40.00
Purified Water, USP, Ph. Eur	Granulating agent	QS*	-	-
Extragranular				
Microcrystalline Cellulose, NF, Ph.Eur., JP (Avicel PH101)	Diluent	5.00	10.00	10.00
Croscarmellose Sodium NF, Ph. Eur., JP (Ac-Di-Sol) SD-711	Disintegrant	4.00	8.00	8.00
Colloidal Silicon dioxide USP/NF, Ph. Eur., JP (Aerosil 200)	Glidant	1.00	2.00	2.00
Magnesium stearate, NF, Ph. Eur., JP (Hyqual 2257)	Lubricant	1.00	2.00	2.00
Total		100.00	200.00	200.00

Table 2 – Formulation Comprising Tildacerfont				
Film Coating				
Opadry II Yellow 85F42129	Film former	3.00	6.00	-
Purified Water, USP, Ph. Eur	Coating dispersion medium	QS*	-	-
Total		100.00	206.00	200.00

Example 3 – Stability of Crystalline Compositions Comprising Compound 1

[00222] To determine the stability of the crystalline compositions prepared comprising the methods described herein, crystalline compositions comprising Compound 1 and oxalic acid were formulated. Samples of the crystalline composition comprising Compound 1-oxalic acid co-crystal were packed in a transparent low-density polyethylene (LDPE) bag, and closed by twisting the bag and tying it with a strip seal. The transparent LDPE bag was then placed in a black LDPE bag that was twisted and tied with a strip seal. The bags were then placed in a high-density polyethylene container.

[00223] The samples were then subjected to accelerated aging conditions (40 ± 2 °C /75 ± 5 % relative humidity (RH)) or long-term storage conditions (25 ± 2 °C / 60 ± 5 % RH). Sample stability measurements in each condition were measured at baseline (before exposure to accelerated aging conditions or long-term storage conditions), and one month, two months, and three months after exposure to said conditions. Sample stability measurements included a description of the sample's physical appearance (e.g., color and form), identification by Fourier-transform infrared spectroscopy (FT-IR), identification by X-ray powder diffraction (XRPD), water content (measured by Karl Fischer (KF) on a % weight/weight basis), identification of related substances (e.g., impurities), and high-performance liquid chromatography ((HPLC) measured on a % weight/weight on an anhydrous basis and solvent free basis).

[00224] **Table 3** summarizes the results of the measurements obtained from samples exposed to the accelerated aging conditions over the course of one to three months. **Table 4** summarizes the results of the study obtained from the samples exposed to the long-term storage conditions over the course of one to three months.

Table 3. Stability data under accelerated aging conditions.

Parameter	Specification	Baseline	1 Month	2 Months	3 Months
Description	Off-white to yellow color solid	Light yellow color solid	Light yellow color solid	Light yellow color solid	Light yellow color solid
Identification by FT-IR	IR spectrum of sample should be concordant with that of reference standard	IR spectrum of sample is concordant with that of reference standard	IR spectrum of sample is concordant with that of reference standard	IR spectrum of sample is concordant with that of reference standard	IR spectrum of sample is concordant with that of reference standard
Identification by XRPD	Diffractogram of the sample should be consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4 ±0.2°	Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4	Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.7, 15.9, 23.4	Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4	Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4
Water Content by KF (% w/w)	NMT 0.5	0.02	0.09	0.02	0.08
Related Substances by HPLC (% area) (see a.-d.)					

a. C07102401-F-Imp1	NMT 0.15	BDRL	BDRL	BDRL	BDRL
b. C07102401-F-Imp2	NMT 0.15	BDRL	BDRL	BDRL	BDRL
c. Any unspecified impurity	NMT 0.10	BDRL	BDRL	BDRL	BDRL
d. Total impurities	NMT 1.0	BDRL	BDRL	BDRL	BDRL
Assay of Compound 1 by HPLC (% w/w on anhydrous basis and solvent free basis)	NLT 98.0 and NMT 102.0	99.9	99.2	100.1	99.2

n/a: not applicable; NLT: not less than; NMT; not more than; BDRL: below disregard limit

[00225] The above data from **Table 3** indicates that the Compound 1-oxalic acid co-crystal is stable up to 3 months at accelerated aging conditions (40 ± 2 °C /75 ± 5 % RH).

Table 4. Stability data under long-term storage conditions.

Parameter	**Specification**	**Baseline**	**1 Month**	**2 Months**	**3 Months**
Description	Off-white to yellow color solid	Light yellow color solid	Light yellow color solid	Light yellow color solid	Light yellow color solid
Identification by FT-IR	IR spectrum of sample should be	IR spectrum of sample is concordant	IR spectrum of sample is concordant	IR spectrum of sample is concordant	IR spectrum of sample is concordant

	concordant with that of reference standard	with that of reference standard	with that of reference standard	with that of reference standard	with that of reference standard
Identification by XRPD	Diffractogram of the sample should be consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4 ±0.2°	Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.8, 10.8, 11.6, 15.9, 23.4	Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 838, 10.8, 11.7, 15.9, 23.4	Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 8.7, 10.8, 11.6, 15.9, 23.3	Diffractogram of the sample is consistent with characteristic 2-θ value of Form-I at 5.4, 837, 10.8, 11.6, 15.9, 23.4
Water Content by KF (% w/w)	NMT 0.5	0.02	0.10	0.03	0.05
Related Substances by HPLC (% area) (see a.-d.)					
a. C07102401-F-Imp1	NMT 0.15	BDRL	BDRL	BDRL	BDRL
b. C07102401-F-Imp2	NMT 0.15	BDRL	BDRL	BDRL	BDRL

c. Any unspecified impurity	NMT 0.10	BDRL	BDRL	BDRL	BDRL
d. Total impurities	NMT 1.0	BDRL	BDRL	BDRL	BDRL
Assay of Compound 1 by HPLC (% w/w on anhydrous basis and solvent free basis)	NLT 98.0 and NMT 102.0	99.9	99.2	100.1	99.2

n/a: not applicable; NLT: not less than; NMT; not more than; BDRL: below disregard limit

[00226] The above data from **Table 4** indicates that the Compound 1-oxalic acid co-crystal is stable up to 3 months at long-term storage conditions (25 ± 2 °C / 60 ± 5 % RH).

Example 4 – Stability of Crystalline Compositions Comprising Compound 1 for 6 Months

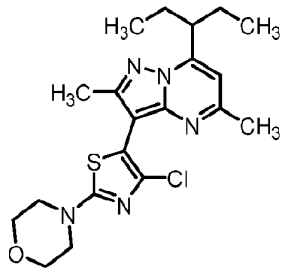
[00227] Samples of the crystalline composition comprising Compound 1-oxalic acid co-crystal prepared in Example 3 are subjected to accelerated aging conditions (40 ± 2 °C /75 ± 5 % relative humidity (RH)) or long-term storage conditions (25 ± 2 °C / 60 ± 5 % RH). Sample stability measurements in each condition are measured at baseline (before exposure to accelerated aging conditions or long-term storage conditions), and four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, fourteen months, sixteen months, and eighteen months after exposure to said conditions. Sample stability measurements include a description of the sample's physical appearance (e.g., color and form), identification by Fourier-transform infrared spectroscopy (FT-IR), identification by X-ray powder diffraction (XRPD), water content (measured by Karl Fischer (KF) on a % weight/weight basis), identification of related substances (e.g., impurities), and high-performance liquid chromatography ((HPLC) measured on a % weight/weight on an anhydrous basis and solvent free basis).

[00228] The samples of the crystalline composition comprising Compound 1-oxalic acid co-crystal will be stable at four months, five months, six months, seven months, eight months,

nine months, ten months, eleven months, twelve months, fourteen months, sixteen months, and eighteen months after exposure to said conditions, as demonstrated by sample stability measurements. Said sample stability measurements at four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, fourteen months, sixteen months, and eighteen months after exposure to said conditions will be in accordance with the results listed in **Table 3** and **Table 4**.

CLAIMS

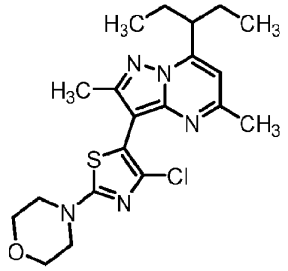
1. A pharmaceutical composition comprising a CRF1 antagonist, wherein the composition is characterized by an X-ray powder diffraction pattern comprising a peak selected from any one or more of 10.84 = 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ.
2. The pharmaceutical composition of claim 1, wherein the composition is measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å .
3. The pharmaceutical composition of claim 1 or 2, wherein the X-ray powder diffraction pattern further comprising at least one peak selected from 5.44 ± 0.2° 2-θ, 20.78 ± 0.2° 2-θ, 22.74 ± 0.2° 2-θ, 23.04 ± 0.2° 2-θ, 26.80 ± 0.2° 2-θ, and 28.86 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.
4. The pharmaceutical composition of any one of claims 1 to 3, wherein the X-ray powder diffraction pattern further comprising at least five peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.
5. The pharmaceutical composition of any one of claims 1 to 4, wherein the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C.
6. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram substantially similar to the one set forth in **FIG. 2**.
7. The pharmaceutical composition of any one of claims 1 to 6, wherein the CRF1 antagonist comprises Compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

8. The pharmaceutical composition of any one of claims 1 to 7, wherein the pharmaceutical composition is a crystalline pharmaceutical composition.
9. The pharmaceutical composition of claim 8, wherein the crystalline pharmaceutical composition further comprises oxalic acid.
10. The pharmaceutical composition of claim 9, wherein the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1.
11. A pharmaceutical composition comprising a CRF1 antagonist, wherein the pharmaceutical composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C.
12. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C.
13. The pharmaceutical composition of claim 11 or 12, wherein the pharmaceutical composition is characterized by a melting point of about 166 °C.
14. The pharmaceutical composition of any one of claims 11 to 13, wherein the CRF1 antagonist comprises Compound 1:

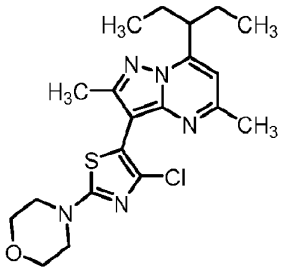


Compound 1

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

15. The pharmaceutical composition of any one of claims 11 to 14, wherein the pharmaceutical composition is a crystalline pharmaceutical composition.
16. The pharmaceutical composition of claim 15, wherein the crystalline pharmaceutical composition further comprises oxalic acid.
17. The pharmaceutical composition of claim 16, wherein the crystalline pharmaceutical composition comprises Compound 1 and oxalic acid in a molar ratio of about 2:1.

18. The pharmaceutical composition of any one of claims 11 to 17, wherein the pharmaceutical composition is further characterized by a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C.
19. A method of preparing a crystalline composition comprising Compound 1:



Compound 1,

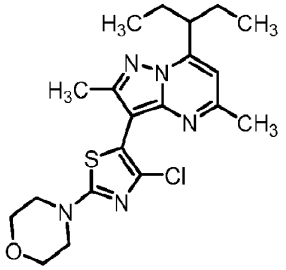
wherein the method comprises:

(a) dissolving Compound 1 and an acid in a solvent;

(b) heating the solution or slurry from step (a); and

(c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Compound 1.

20. The method of claim 19, wherein the acid comprises oxalic acid.
21. The method of claim 19 or 20, wherein the solvent in step (a) is heptane.
22. The method of claim 19 or 20, wherein the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone.
23. The method of claim 19 or 20, wherein the solvent in step (a) is a mixture of heptane and methyl ethyl ketone.
24. The method of any one of claims 19 to 23, wherein step (b) is heated at about 50 °C.
25. A pharmaceutical composition comprising Compound 1:



Compound 1, or a pharmaceutically acceptable salt or solvate thereof,

wherein Compound 1 is present in an amount of 25% w/w; and

a diluent in about 5% to about 70%

26. The pharmaceutical composition of claim 25, wherein Compound 1 is in an amount of about 50 mg to about 200 mg.
27. The pharmaceutical composition of claim 25, wherein Compound 1 is in an amount of about 50 mg.
28. The pharmaceutical composition of claim 25, wherein the diluent is selected from the group consisting of calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose monohydrate, and a combination thereof.
29. The pharmaceutical composition of claim 28, wherein the diluent is lactose monohydrate.
30. The pharmaceutical composition of claim 29, wherein the lactose monohydrate is about 20% to about 45% by weight of the pharmaceutical composition.
31. The pharmaceutical composition of claim 29, wherein the lactose monohydrate is about 20% to about 40.25% by weight of the pharmaceutical composition.
32. The pharmaceutical composition of claim 31, wherein the lactose monohydrate is in an amount that is about 16.1, 40.25, 80.5, or 322 mg.
33. The pharmaceutical composition of claim 28, wherein the diluent is microcrystalline cellulose.
34. The pharmaceutical composition of claim 28, further comprising a second diluent, wherein the second diluent comprises microcrystalline cellulose
35. The pharmaceutical composition of claim 33, wherein the microcrystalline cellulose is about 25% by weight of the pharmaceutical composition.
36. The pharmaceutical composition of claim 35, wherein the microcrystalline cellulose is in an amount that is about 50 mg.
37. The pharmaceutical composition of claim 25, further comprising a binder, wherein the binder is selected from the group consisting of corn starch and potato starch, gelatin, sucrose hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC), and a combination thereof.
38. The pharmaceutical composition of claim 37, wherein the binder comprises HPC.
39. The pharmaceutical composition of claim 38, wherein the HPC is about 3% by weight of the solid dosage form.

40. The pharmaceutical composition of claim 25, further comprising a surfactant, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate, tetradecyl trimethyl ammonium bromide with dodecyl, hexadecyl compound, benzalkonium chloride, cetylpyridinium chloride, alkylsulphate, alkylethoxylate sulphate, soap, carxylate ion, sulfate ion, sulfonate ion, polyoxyethylene derivative, polyoxypropylene derivative, polyol derivative, polyol ester, polyoxyethylene ester, poloxamers, glocol, glycerol ester, sorbitan derivative, and polyethylene glycol, and a combination thereof.

41. The pharmaceutical composition of claim 40, wherein the surfactant comprises sodium lauryl sulfate.

42. The pharmaceutical composition of claim 41, wherein the sodium lauryl sulfate is about 0.75% by weight of the solid dosage form.

43. The pharmaceutical composition of claim 42, wherein the sodium lauryl sulfate is in an amount that is about 1.5 mg.

44. The pharmaceutical formulation of claim 25, further comprising a disintegrant, wherein the disintegrant is selected from the group consisting of starch, alginic acid, ac-di-sol, croscarmellose sodium, sodium starch glycolate, and crospovidone, and a combination thereof.

45. The pharmaceutical formulation of claim 44, wherein the disintegrant comprises croscarmellose sodium.

46. The pharmaceutical formulation of claim 25, further comprising a glidant, wherein the glidant comprises colloidal silicon dioxide.

47. The pharmaceutical formulation of claim 46, wherein the colloidal silicon dioxide is about 1% by weight of the solid dosage form.

48. The pharmaceutical formulation of claim 46, wherein the colloidal silicon dioxide is in an amount that is about 2 mg.

49. The pharmaceutical formulation of claim 25, further comprising a lubricant, wherein the lubricant is selected from the group consisting of talc, stearic acid, magnesium stearate, sodium stearyl fumarate, and a combination thereof.

50. The pharmaceutical formulation of claim 25, wherein the pharmaceutical formulation is in a solid dosage form.

51. The pharmaceutical formulation of claim 50, wherein the solid dosage form is a tablet.

52. The pharmaceutical formulation of claim 50, wherein the solid dosage form is a granules form.

53. The pharmaceutical formulation of claim 52, wherein said granules form is packaged in a capsule.

54. The pharmaceutical formulation of claim 52, wherein said granules form is packaged in a sachet.

55. A pharmaceutical formulation, comprising:

(a) about 10 mg to about 300 mg of 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-α) pyrimidine (Compound 1), or a pharmaceutically acceptable salt or solvate thereof;

(b) a first diluent in about 40% to about 45% by weight, wherein the first diluent comprises lactose monohydrate;

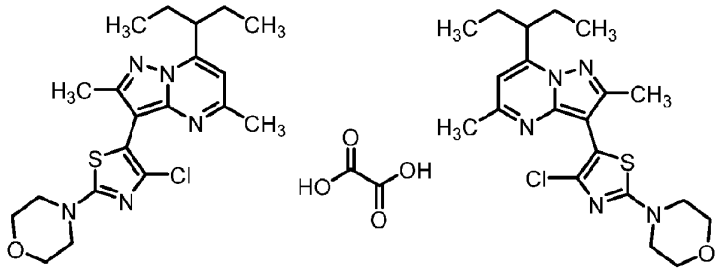
(c) a second diluent in about 25% by weight, wherein the second diluent comprises microcrystalline cellulose;

(d) about 1% to about 6% by weight of hydroxypropyl cellulose;

(e) about 0.5% to about 5% by weight of sodium lauryl sulfate; and

(f) about 4% by weight of croscarmellose sodium.

56. A crystalline composition comprising Formula I:



Formula I.

57. The crystalline composition of claim 56, wherein the crystals have unit cell parameters at T = 150°K of: a = 34.003(4) Å, b = 6.5843(13) Å, c = 21.062(5) Å; β = 108.703(12)°, V = 4466.5(15) $Å^3$ and a monoclinic C2/c space group.

58. The crystalline composition of claim 56, wherein the crystalline composition is characterized by:

(a) an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å;

(b) an X-ray powder diffraction pattern substantially the same as shown in FIG. 1;

(c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C;

(d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C;

(e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2;

(f) a thermogravimetric analysis (TGA) thermogram comprising a loss in mass of about 11% over a temperature range of about 25 °C to about 200 °C;

(g) a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3; or

(h) combinations thereof.

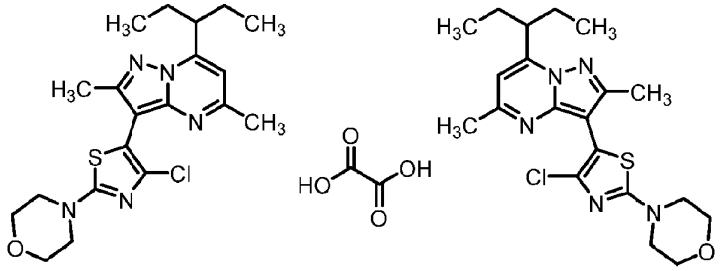
59. The crystalline composition of any one of claim 56, wherein the crystalline composition is characterized by an X-ray powder diffraction pattern comprising peaks at 10.84 ± 0.2° 2-θ, 15.96 ± 0.2° 2-θ, 23.44 ± 0.2° 2-θ, and 24.80 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

60. The crystalline composition of claim 59, wherein the X-ray powder diffraction pattern further comprising at least one peak selected from 5.44 ± 0.2° 2-θ, 20.78 ± 0.2° 2-θ, 22.74 ± 0.2° 2-θ, 23.04 ± 0.2° 2-θ, 26.80 ± 0.2° 2-θ, and 28.86 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

61. The crystalline composition of claim 59, wherein the X-ray powder diffraction pattern further comprising at least five peaks selected from 8.82 ± 0.2° 2-θ, 11.70 ± 0.2° 2-θ, 14.60 ± 0.2° 2-θ, 15.56 ± 0.2° 2-θ, 16.70 ± 0.2° 2-θ, 18.82 ± 0.2° 2-θ, 19.18 ± 0.2° 2-θ, 20.02 ± 0.2° 2-θ, 20.50 ± 0.2° 2-θ, 21.72 ± 0.2° 2-θ, 25.52 ± 0.2° 2-θ, 25.92 ± 0.2° 2-θ, 26.94 ± 0.2° 2-θ, and 28.00 ± 0.2° 2-θ, and as measured by X-ray powder diffraction using an X-ray wavelength of 0.71073 Å.

62. The crystalline composition of any one of claims 56 to 61, wherein the crystalline composition is characterized by an X-ray powder diffraction pattern substantially the same as shown in FIG. 1.

63. The crystalline composition of any one of claims 56 to 62, wherein the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160 °C to 170 °C.
64. The crystalline composition of any one of claims 56 to 62, wherein the crystalline composition is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 164 °C and a peak of about 166 °C.
65. The crystalline composition of any one of claims 56 to 64, wherein the crystalline composition is characterized by a melting point of about 166 °C.
66. The crystalline composition of any one of claims 56 to 65, wherein the crystalline composition if characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2.
67. The crystalline composition of any one of claims 56 to 66, wherein the crystalline composition is characterized by a thermogravimetric analysis (TGA) thermogram substantially the same as shown in FIG. 3.
68. The crystalline composition of any one of claims 56 to 67, wherein the crystalline composition is characterized by a dynamic vapor sorption (DVS) trace substantially the same as shown in FIG. 4.
69. A method of preparing a crystalline composition comprising Formula I:



Formula I,

wherein the method comprises:

(a) dissolving 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine (Compound 1) and oxalic acid in a solvent;

(b) heating the solution or slurry from step (a); and

(c) crystallizing the solution or slurry obtained in step (b) to obtain the crystalline composition comprising Formula I.

70. The method of claim 69, wherein the solvent in step (a) comprises acetone, heptane, water, 2-butanol, ethyl acetate, 2-propanol, methyl tert-butyl ether, ethanol, methyl ethyl ketone, 1-pentanol, or a combination thereof.
71. The method of claim 70, wherein the solvent in step (a) is heptane.
72. The method of claim 70, wherein the solvent in step (a) is methyl tert-butyl ether or methyl ethyl ketone.
73. The method of claim 70, wherein the solvent in step (a) is a mixture of heptane and methyl ethyl ketone.
74. The method of claim 69, wherein step (b) is heated at about 50 °C.
75. A method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART) in a subject in need thereof, comprising administering the subject the crystalline composition of any one of the preceding claims.
76. The method of claim 75, wherein the subject has congenital adrenal hyperplasia (CAH).
77. A method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
78. The method of claim 77, wherein the CAH is classic CAH.
79. The method of claim 77, wherein the CAH is non-classical CAH.
80. A method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
81. The method of claim 80, wherein the hyperandrogenic symptoms are selected from the group consisting of acne, hirsutism, and alopecia.
82. A method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
83. A method of improving metabolic symptoms in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
84. The method of claim 83, wherein the metabolic symptoms are selected from the group consisting of body weight, BMI, fat mass, waist circumference, blood pressure and glycemic control.
85. A method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a

subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.

86. A method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, administering to the subject the crystalline composition of any one of the preceding claims.
87. A method of treating endometriosis or improving the symptoms of endometriosis in a subject in need thereof, comprising administering to the subject the crystalline composition of any one of the preceding claims.
88. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition improves the symptom of pain experienced by the subject.
89. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition reduces the symptom of pain experienced by the subject.
90. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition prevents the symptom of pain experienced by the subject.
91. The method of claim 87, wherein the administration of the crystalline composition or the pharmaceutical composition eliminates the symptom of pain experienced by the subject.
92. The method of any one of claims 75 to 87, wherein the crystalline composition or the pharmaceutical composition is administered at a dose from about 5 mg/day to about 1000 mg/day.
93. The method of any one of claims 75 to 92, wherein the crystalline composition or the pharmaceutical composition is 75to in a fed state.
94. The method of any one of claims 75 to 92, wherein the crystalline composition or the pharmaceutical composition is administered in a fasted state.
95. The method of any one of claims 75 to 94, wherein the crystalline composition or the pharmaceutical composition is administered at least once per day.
96. The method of any one of claims 75 to 95, furthering comprising administering to the subject an additional therapeutic agent.
97. The method of anyone of the preceding claims, wherein the method further comprises administering an additional therapeutic agent, wherein the additional therapeutic agent is glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen agent.
98. The method of claim 97, wherein the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone.
99. The method of claim 97, wherein the mineralocorticoid is fludrocortisone.

100. The method of claim 97, wherein the additional therapeutic agent is another CRF_1 antagonist.

101. The method of any one of claims 75 to 100, further comprising an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

102. The method of claim 101, wherein the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the crystalline composition of any one of the preceding claims.

103. The method of any one of claims 75 to 97, wherein the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the crystalline composition of any one of the preceding claims.

104. The method of any one of the preceding claims, wherein the subject is from about 9 years of age to about 18 years of age.

105. The method of any one of the preceding claims, wherein the subject is from about 8 years of age to about 55 years of age.

FIG. 1

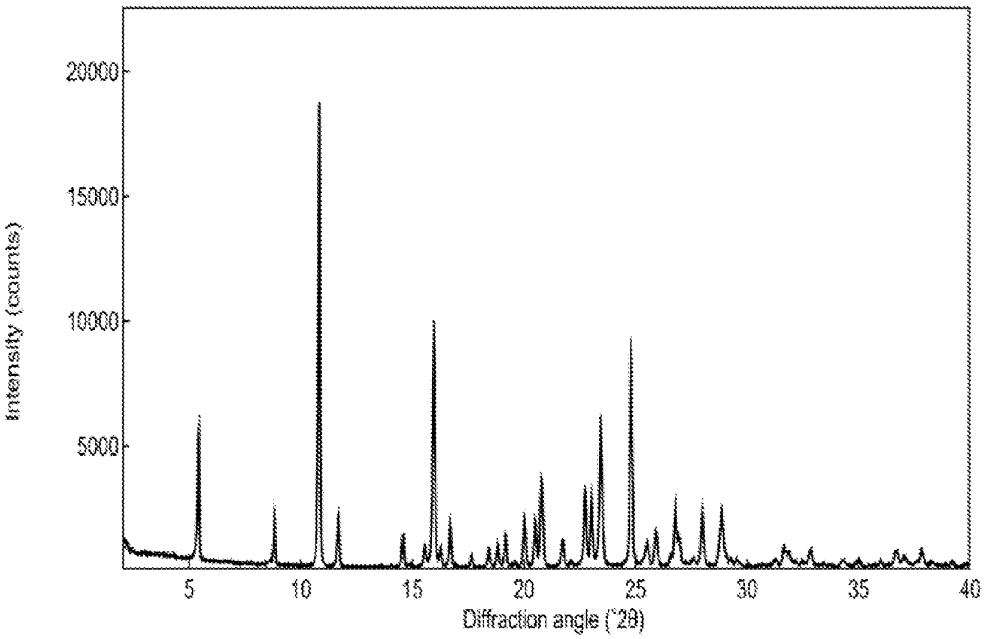

20000
15000
10000
5000
Intensity (counts)
5
10
15
20
25
30
35
40
Diffraction angle (°2θ)

FIG. 2

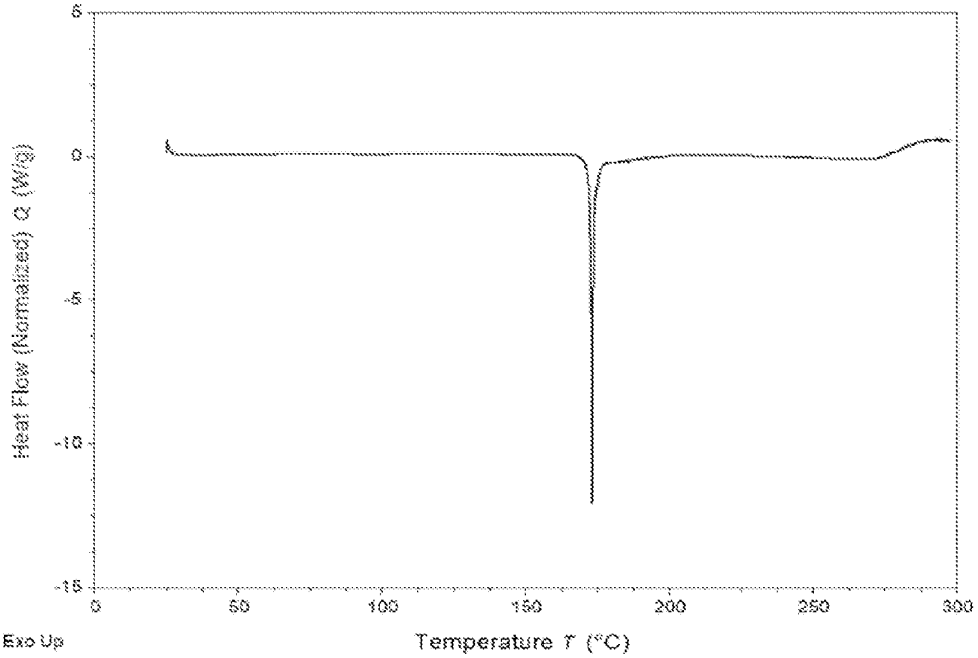

5
0
-5
-10
-15
Heat Flow (Normalized) Q (W/g)
0
50
100
150
200
250
300
Exo Up
Temperature T (°C)

FIG. 3

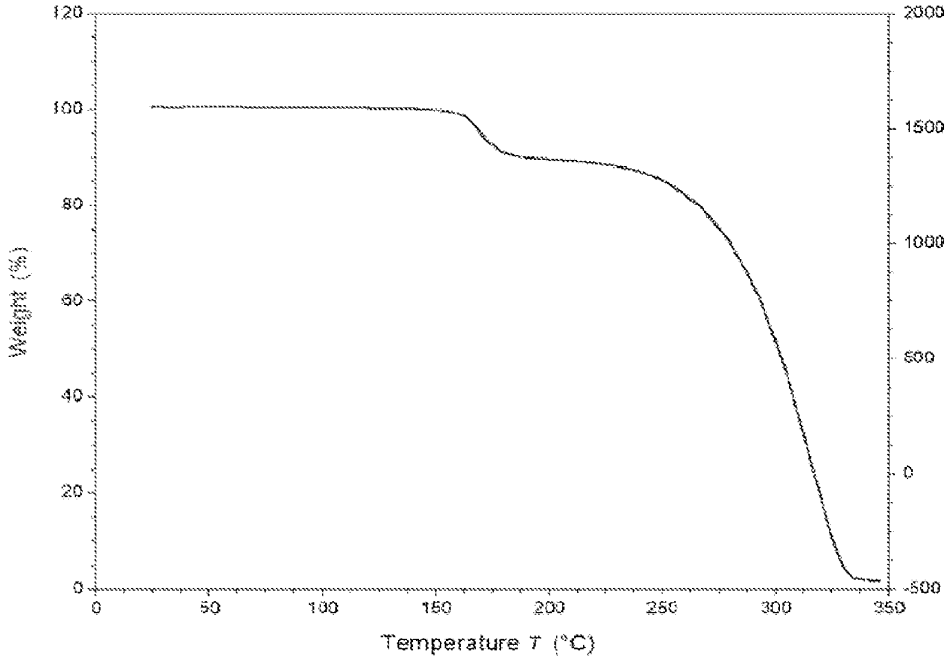

120
100
80
60
40
20
0
Weight (%)
2000
1500
1000
500
0
-500
0
50
100
150
200
250
300
350
Temperature T (°C)

FIG. 4

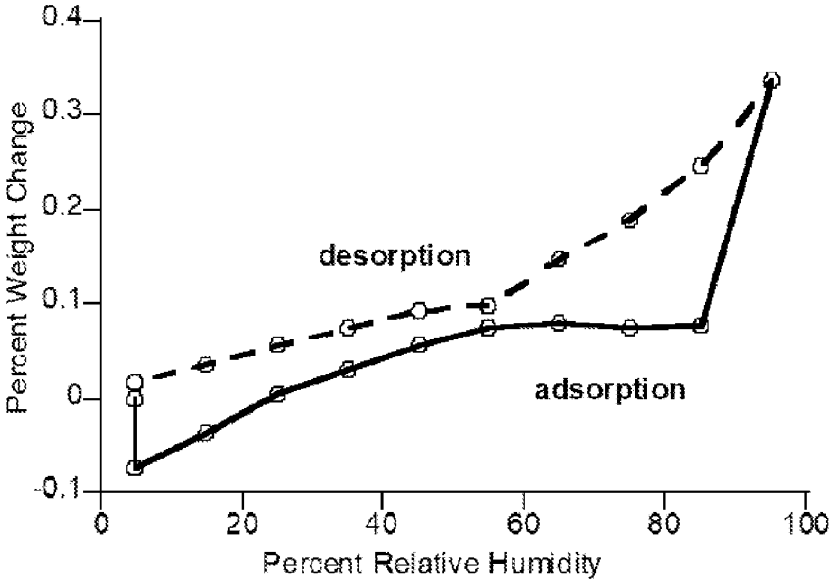

0.4
0.3
0.2
0.1
0
-0.1
Percent Weight Change
desorption
adsorption
0
20
40
60
80
100
Percent Relative Humidity

FIG. 5

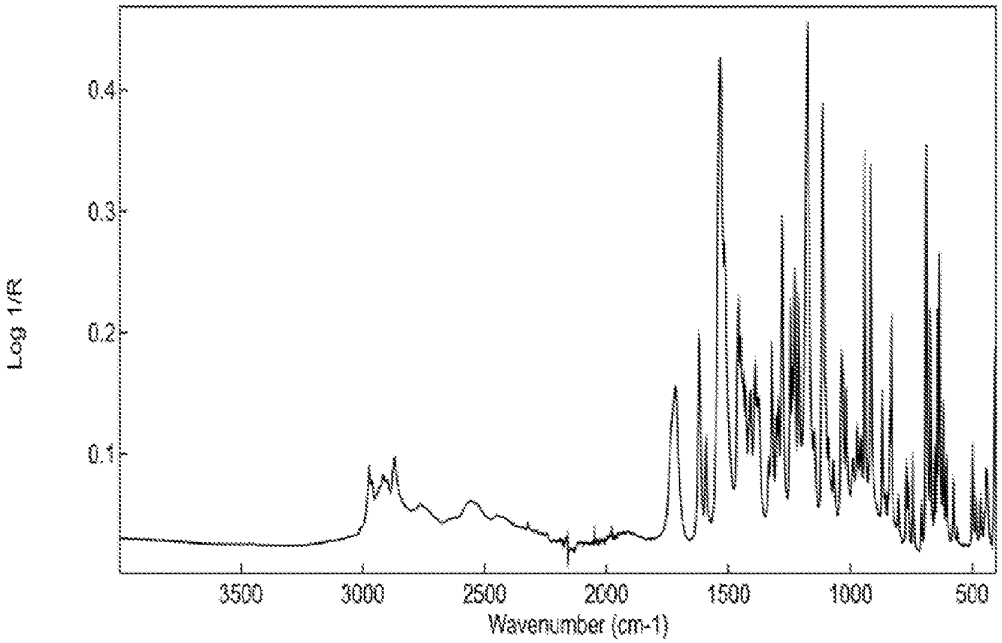

Log 1/R
0.4
0.3
0.2
0.1
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

FIG. 6

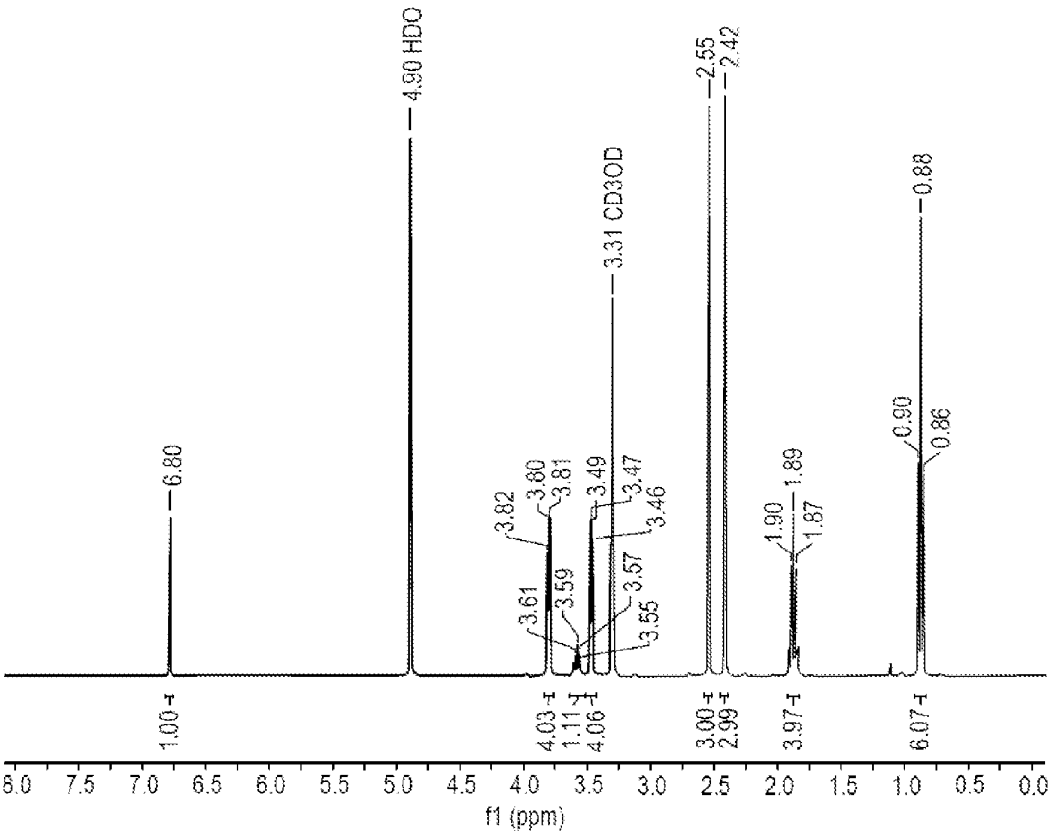
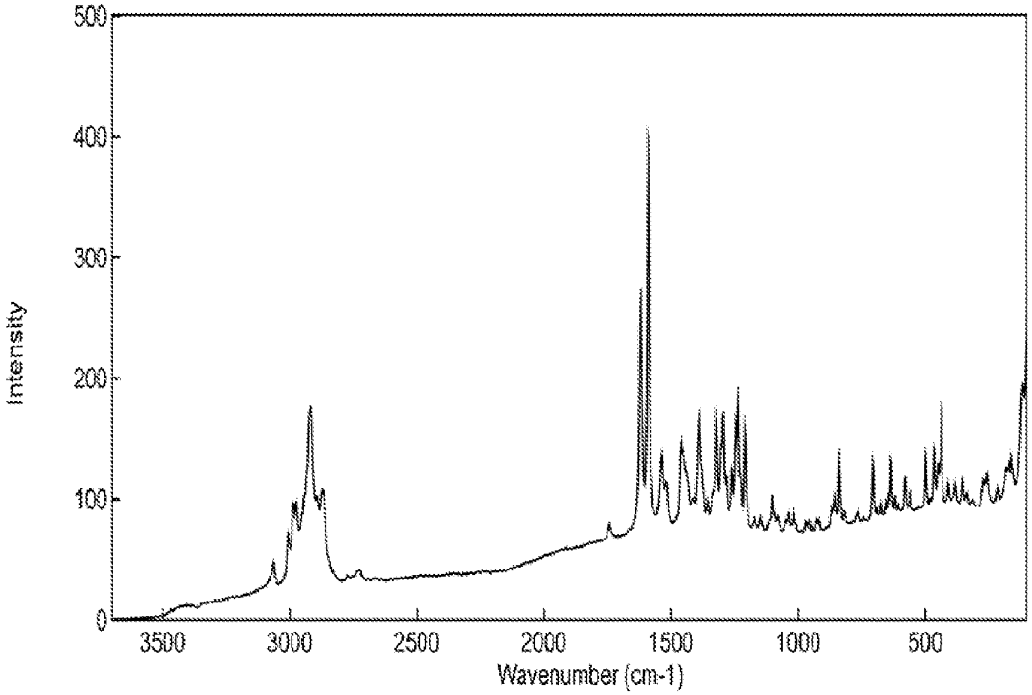

4.90 HDO
3.31 CD3OD
2.55
2.42
0.88
6.80
3.82
3.80
3.81
3.49
3.47
3.46
3.61
3.59
3.57
3.55
1.90
1.89
1.87
0.90
0.86
1.00
4.03
1.11
4.06
3.00
2.99
3.97
6.07
f1 (ppm)

FIG. 7


500
400
300
200
100
0
Intensity
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/050436

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/050436

A. CLASSIFICATION OF SUBJECT MATTER

C07D 487/04 (2006.01) A61K 31/5377 (2006.01) A61K 47/12 (2006.01) A61K 9/00 (2006.01) A61P 5/38 (2006.01) A61P 15/08 (2006.01) A61P 5/24 (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

Google, EPOQUE and STN Search - PATENW, BIOSIS, CAPLUS, EMBASE, MEDLINE, REGISTRY; Keywords – tildacerfont, oxalic acid, corticotropin releasing factor, CRHR1, CRF1, congenital adrenal hyperplasia, CAH, and related terms

Applicant/Inventor Search - Espacenet, PubMED, AusPAT, Google Patents, IP Australia Internal Databases, REDDY, Dasharatha; RAJAGOPAL, Ashokraj; WANG, Lu; BARNES, Christopher; SPRUCE BIOSCIENCES, INC.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2023	20 February 2023

Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Anthony Lai AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 6283 2642

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

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **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 IJ, Merke DP, Moriarty D, Nakhle S, Newfield RS, Vogiatzi MG, Auchus RJ. Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies. J Clin Endocrinol Metab. 2021 Oct 21;106(11):e4666-e4679. doi: 10.1210/clinem/dgab438. 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

Continuation of: **Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1-24 and 56-74 (in full), and claims 75-105 (in part) are directed to compositions comprising a salt crystal form of tildacerfont, wherein the feature of the salt crystal form of tildacerfont is specific to this group of claims
- Claims 25-55 (in full), and claims 75-105 (in part) are directed to compositions comprising tildacerfont available in any form, wherein the feature of tildacerfont is specific to this group of claims

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions and which provides a technical relationship among them is tildacerfont

However it is considered that this feature is generic in this particular art. Therefore in this light this common feature cannot be a special technical feature. Hence there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied a *priori*.

INTERNATIONAL SEARCH REPORT 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**
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
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		BR PI0717023 B1	19 Nov 2019
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		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.

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.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 September 2006 (28.09.2006)

PCT

(10) International Publication Number
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A61K 31/5025 (2006.01)

(21) International Application Number:
PCT/US2006/009942

(22) International Filing Date: 20 March 2006 (20.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/663,816 21 March 2005 (21.03.2005) US

(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BARBOSA, Heather, Janelle** [US/US]; 7230 Forrester Lane, Indianapolis, Indiana 46217 (US). **COLLINS, Elizabeth, Aaron** [US/US]; 8374 South Private Drive 435 West, Edinburgh, Indiana 46124 (US). **HAMDOUCHI, Chafiq** [ES/US]; 14469 Twin Oaks Drive, Carmel, Indiana 46032 (US). **HEMBRE, Erik, James** [US/US]; 1332 North New Jersey Street, Indianapolis, Indiana 46202 (US). **HIPSKIND, Philip, Arthur** [US/US]; 4255 Cabin Court, New Palestine, Indiana 46163 (US). **JOHNSTON, Richard, Duane** [US/US]; 3712 Forest Lane, Greenfield, Indiana 46140 (US). **LU, Jianliang** [CN/US]; 11921 Castlestone Drive, Fishers, Indiana 46307 (US). **RUPP, Michael, John** [US/US]; 10003 Scotch Pine Lane, Indianapolis, In 46256 (US). **TAKAKUWA, Takako** [JP/US]; 7653 Germander Lane, Indianapolis, Indiana 46237 (US). **THOMPSON, Richard, Craig** [US/US]; 763 North County Road 900 West, Frankfort, Indiana 46041 (US).

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

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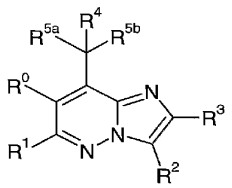
(54) Title: IMIDAZOPYRIDAZINE COMPOUNDS



(I)

(57) Abstract: The present invention relates to novel substituted imidazo[1,2-b]pyridazine compounds of Formula (I): pharmaceutical compositions thereof, and the use such compounds as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric disorders and neurological diseases.

WO 2006/102194 A1

IMIDAZOPYRIDAZINE COMPOUNDS

Field of the Invention

This 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 disorders and neurological diseases.

Background of the Invention

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 [J. Rivier et al., *Proc. Natl. Acad. Sci (USA)* 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in 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 [J. E. Blalock, *Physiological Reviews* 69:1 (1989); J. E. Morley, *Life Sci.* 41:527 (1987)].

There is 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 a review, see: E. B. De Souze, *Hosp. Practice* 23:59 (1988)]. Furthermore, CRF is known to have a broad extrahypothalmic distribution in the CNS, contributing therein to a wide spectrum of autonomic behavioral and physiological effects [see, e.g., Vale et al., 1983; Koob, 1985; and E. B. De Souze et al., 1985]. For example,

CRF concentrations are significantly increased in the cerebral spinal fluid of patients afflicted with affective disorder or major depression [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)]. Moreover, excessive levels of CRF are known to produce anxiogenic effects in animal models [see, e.g., Britton et al., 1982; Berridge and Dunn, 1986 and 1987].

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 (intravenously 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 Engl. 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 also preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of receptors in the brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

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 both in 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 Ro 15-1788, 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 FG 7142 enhanced the actions of CRF [K. T. Britton et al., *Psychopharmacology* 94:396 (1988)]. Preliminary studies using the putative CRF receptor antagonist α-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrates 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)].

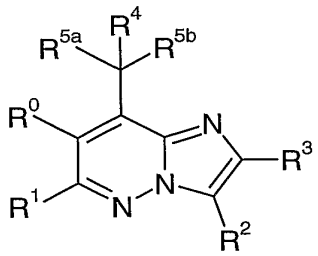
CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain [D. T. Chalmers et al., *TIPS* 17:166-72 (1996)] thereby suggesting potential functional diversity [S. C. Heinrichs et al., *Regul. Peptides* 71:15 (1997)]. For example, widely distributed 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 et al., 1997]. A more discrete septal/hypothalmic 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 an altogether 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 appetite without producing the profile of behavioral activation observed with selective CRF1 agonism (H. Tezval et al., *PNAS* 101(25): 9468-9473 (2004)]. In many 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)]. While CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well [C. Contoreggi et al., *Neuroendocrinology* 80(2):111-23 (2004)].

In view of the above, efficacious and selective antagonists of CRF1 are desired as potentially valuable therapeutic agents for the treatment of psychiatric disorders and neurological diseases. It is thus desirable to discover new CRF1 antagonists.

SUMMARY OF THE INVENTION

The compounds of the present invention include CRF1 receptor antagonists.

One embodiment of the present invention is a compound of Formula I:



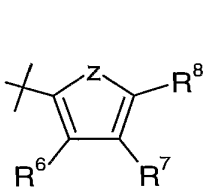
Formula I

wherein:

R^0 is hydrogen, halo, methyl or ethyl;

R^1 and R^3 are independently methyl, methoxy, or trifluoromethyl;

R^2 is selected from the group consisting of: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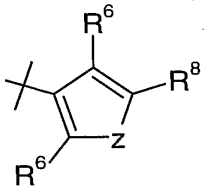
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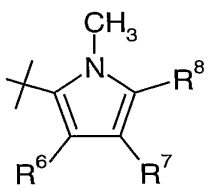
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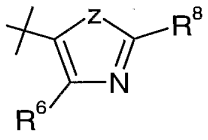
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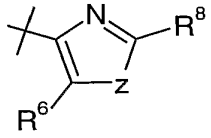
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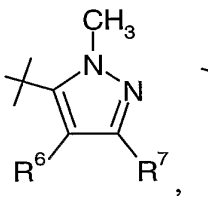
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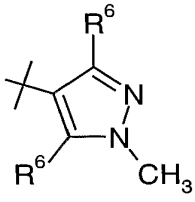
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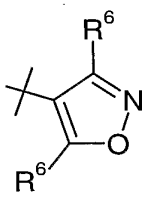
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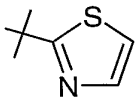
R^4 is hydrogen, halo, or hydroxy;

R^{5a} and R^{5b} are independently ethyl or n-propyl;

R^6 at each occurrence is independently hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, trifluoromethyl, methoxy, or phenyl;

R^7 is hydrogen, halo, methyl, methoxy, dimethylamino,

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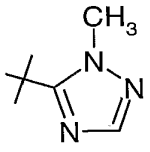
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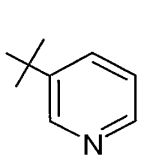
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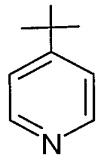
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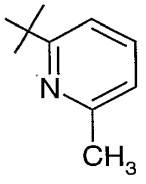
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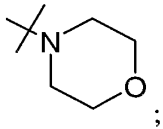
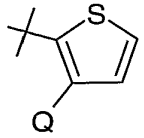

;

R^8 is selected from the group consisting of hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, R^aR^bN-, carbamyl, $(C_1\text{-}C_2)$alkoxy$(C_1\text{-}C_2)$alkyl, R^{11}-C(O)-,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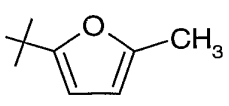
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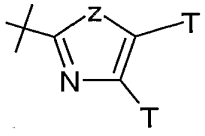
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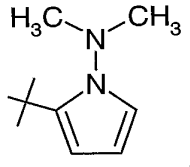
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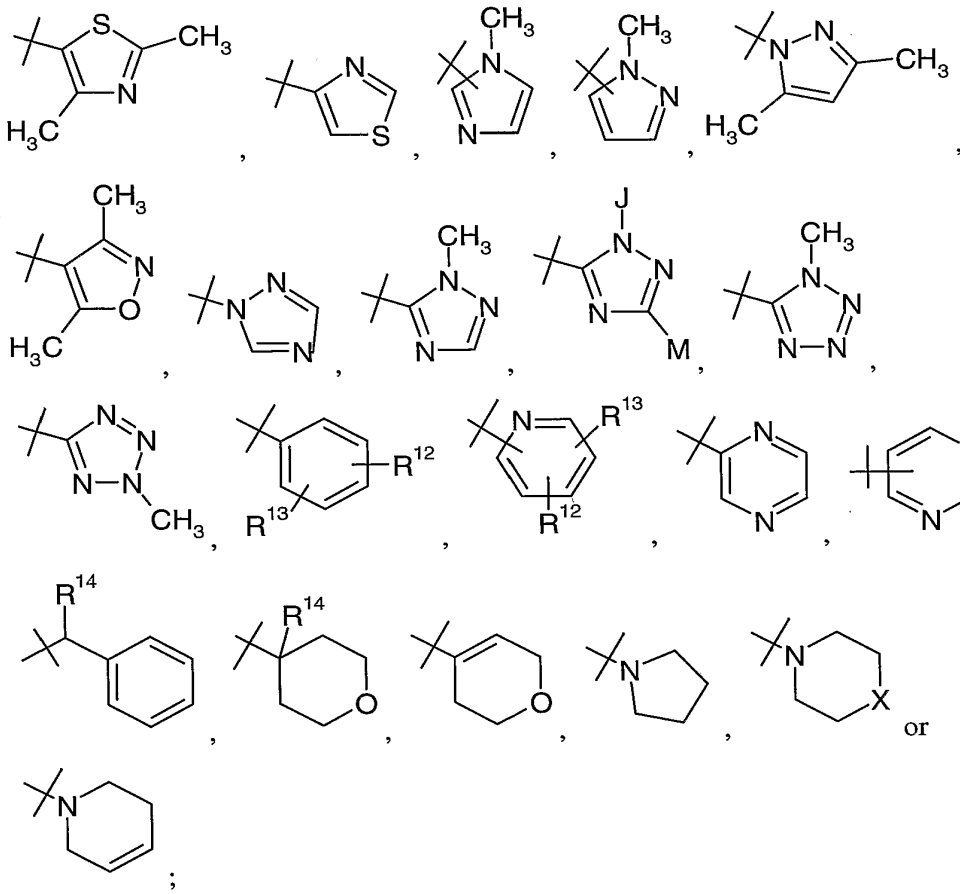


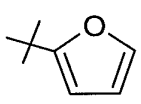
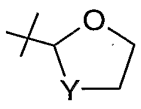
;

R^{11} is methoxy, methylamino, dimethylamino, or phenyl;

R^{12} is hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy dimethylamino, acetyl, or methylsulfonyl;

R^{13} is hydrogen, methyl or halo;

R^{14} is hydrogen or hydroxy;

R^{15} is methylthio, cyclopropyl, phenyl,  or  ;

R^a is hydrogen, $(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_5)$cycloalkyl, methoxy$(C_2\text{-}C_4)$alkyl, acetyl, $(C_1\text{-}C_2)$alkylsulfonyl, (C_3)alkenyl, $R^{15}\text{-}(CH_2)n\text{-}$, or $(C_1\text{-}C_2)$alkyl substituted with cyano, formyl, vinyl, or ethynyl;

R^b is hydrogen or $(C_1\text{-}C_3)$alkyl;

X is $-CH_2-$, -CO-, -O-, -S- or $-SO_2-$;

Y is -CH_2- or -O-;

z is S or O;

n is 1 or 2;

Q is hydrogen or methyl;

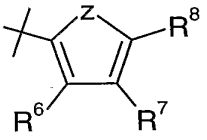
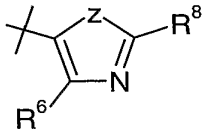
T is hydrogen or methyl;

J is methyl, trifluoroethyl, or tert-butyl; and

M is methyl or halo;

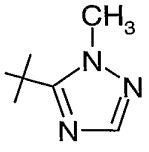
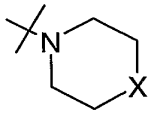
and pharmaceutically acceptable salts thereof.

Another embodiment of the present invention is a compound of Formula I wherein R^0 and R^4 are hydrogen, R^1 and R^3 are methyl, and R^{5a} and R^{5b} are ethyl.

Yet another embodiment of the present invention is a compound of Formula I wherein R^2 is selected from the group consisting of  or  where z is S.

A further embodiment of the present invention is a compound of Formula I wherein R^7 is hydrogen.

Another another embodiment of the present invention is a compound of Formula I wherein R^6 is halo or methyl.

Yet another embodiment of the present invention is a compound of Formula I wherein R^8 is  or  where X is O.

Another embodiment of the present 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 use of a compound of Formula I for the manufacture of a medicament for treating anxiety, depression, major depressive disorder, alcohol withdrawal symptoms, or irritable bowel syndrome in a mammal. In another further embodiment, the mammal is a human.

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:

"Alkoxy" means an alkyl-O- group, wherein the alkyl group is as herein described. Exemplary 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" means a monocyclic group, having 3 to 5 carbon atoms.

"Halo" means fluoro, chloro, bromo, or iodo.

"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 isolating the salt thus formed. Exemplary acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, sulphamates, malonates, salicylates, propionates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinateslaurylsulphonate salts, and the like. See, for example S.M. Berge, et al.,

"Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977). Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing. Company, Easton, Pa., 1985, p. 1418.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts thereof.

"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 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 or 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 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 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 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 toward the point of attachment. For example, an arylcarbonylaminoalkyl substituent is equivalent to aryl-C(O)-NH-alkyl-.

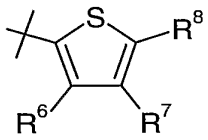
The present invention contemplates specific classes of compounds of Formula I. The following paragraphs describe such specific classes:

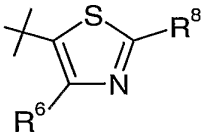
(a) R^0 is hydrogen;

(b) R^1 is methyl;

(c) R^3 is methyl;

(d) $R^1$and R^3 are methyl;

(e) R^2 is  ;

(f) R^2 is  ;

(g) R^4 is hydrogen;

(h) R^{5a} is ethyl;

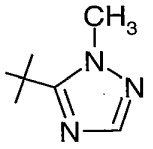
(i) R^{5b} is ethyl;

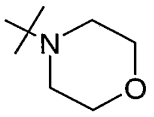
(j) R^{5a} and R^{5b} are ethyl;

(k) R^6 is halo;

(l) R^6 is methyl;

(m) R^7 is hydrogen;

(n) R^8 is  ;

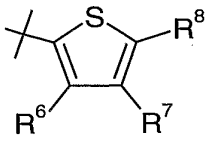
(o) R^8 is  .

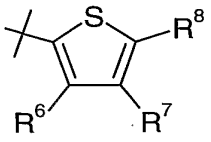
While all the compounds of Formula I are useful CRF1 receptor antagonists, the following paragraphs describe further specific classes:

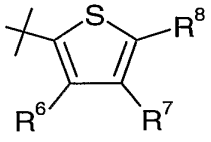
(a) Each of R^1 and R^3 is methyl and each of R^{5a} and R^{5b} is ethyl;

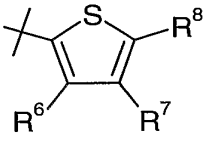
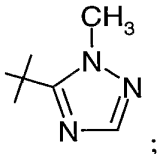
(b) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 is hydrogen;

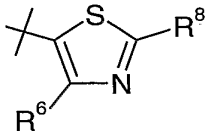
(c) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen;

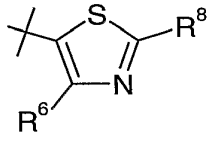
(d) R^2 is  and R^7 is hydrogen;

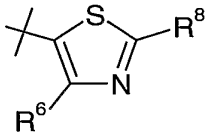
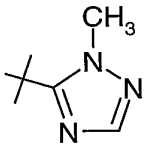
(e) R^2 is  , R^7 is hydrogen, and R^6 is halo;

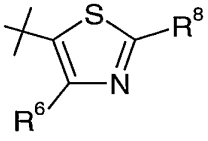
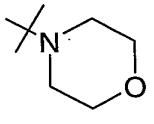
(f) R^2 is  , R^7 is hydrogen, and R^6 is methyl;

(g) R^2 is  , R^7 is hydrogen, and R^6 is halo or methyl, and R^8 is  ;

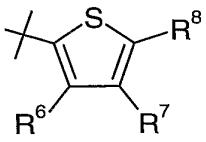
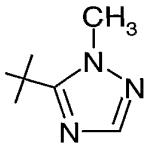
(h) R^2 is  and R^6 is halo;

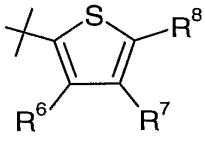
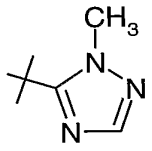
(i) R^2 is  and R^6 is methyl;

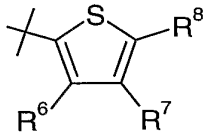
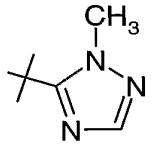
(j) R^2 is  , R^6 is halo or methyl, and R^8 is  ;

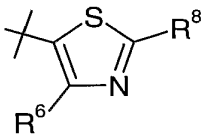
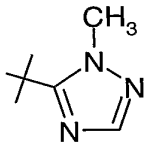
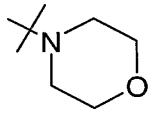
(k) R^2 is  , R^6 is halo or methyl, and R^8 is  .

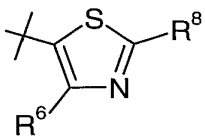
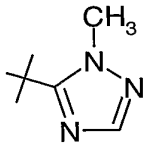
The following paragraphs describe even more specific classes of CRF1 receptor antagonists of the invention:

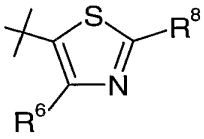
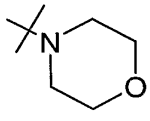
(a) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is halo or methyl, and R^8 is  ;

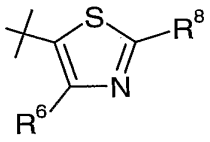
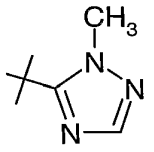
(b) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is halo, and R^8 is  ;

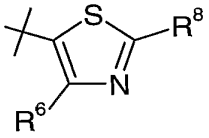
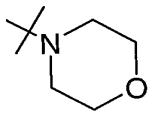
(c) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is methyl, and R^8 is  ;

(d) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo or methyl, and R^8 is  or  ;

(e) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo, and R^8 is  ;

(f) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo, and R^8 is  .

(g) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is methyl, and R^8 is  ;

(h) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is methyl, and R^8 is  .

Preferably compounds of the invention exhibit a Ki value for CRF1 binding of 1 micromolar or less, more preferably of 500 nanomolar or less. Even more preferably, compounds of the invention exhibit a Ki value for CRF1 binding of 250 nanomolar or less, with 100 nanomolar or less being even further preferred. With even greater preference, compounds of the invention exhibit a Ki value for CRF1 binding of 30 nanomolar or less, while 15 nanomolar or less is even more greatly preferred. Compounds of the invention exhibiting a Ki value for CRF1 binding of 5 nanomolar or less are most preferred.

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 medium generally accepted in the art for the delivery of biologically active agents to mammals, e.g., humans. Such carriers are generally formulated according to a number of factors well within the purview of those of ordinary skill in the art to determine and account for. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers and excipients include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi- solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, e.g., stabilization of the active agent, well known to those of ordinary skill in the art. Descriptions of suitable

pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources, e.g., Remington's Pharmaceutical Sciences, 17 th ed., Mack Publishing Company, Easton, Pa., 1985.

These compounds of formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Dosage forms suitable 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 ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of formula I are antagonists at 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, that includes phobic disorders, anxiety states, post-traumatic stress disorder and atypical anxiety disorders [The Merck Manual of Diagnosis and Therapy, 16 th edition (1992)]. Emotional stress is often a precipitating factor in anxiety disorders, and such disorders generally respond to medications that lower response to stress. The compounds are also useful in smoking cessation programs. The method of treatment involves administration to a mammal (e.g. a human) an effective amount of a compound of the invention. In particular, therapeutically effective amounts of the compounds of this invention are amounts effective to antagonize, or lower, levels of corticotropin releasing factor (CRF) in a mammal (e.g. a human), thereby alleviating in the mammal's conditions characterized by abnormally high levels of CRF expression.

As such, the present invention provides a method for treating a condition which is treatable by reducing CRF1 receptor stimulation, comprising administering to the mammal (e.g. a human) in need thereof a compound of Formula I, or a pharmaceutically acceptable salt thereof, in an amount effective to antagonize CRF1 receptor stimulation.

The present invention also provides use of a compound of Formula I for the manufacture of a medicament for treating a condition which is treatable by reducing CRF1 receptor stimulation.

The present invention also provides a method of antagonizing CRF1 receptors in a warm-blooded animal, comprising administering to the animal a compound of the invention at amount effective to antagonize CRF1 receptors. The warm-blooded animal is preferably a mammal, and more preferably a human.

The present invention also provides a method of treating a disorder in a warm-blooded animal, which disorder manifests hypersecretion of CRF, or the treatment of which disorder can be effected or facilitated by antagonizing CRF1 receptors, comprising administering to the animal a therapeutically effective amount of a compound of the invention. The warm-blooded animal is preferably a mammal, and more preferably a human.

Compounds of Formula I, or a pharmaceutically acceptable salt thereof, are useful for treating various disorders and conditions in a mammal (e.g. human) including social anxiety disorder; panic disorder; obsessive-compulsive disorder; major depressive disorder; anxiety with co-morbid depressive illness; affective disorder; anxiety; depression; irritable bowel syndrome; post-traumatic stress disorder; supranuclear palsy; immune suppression; gastrointestinal disease; anorexia nervosa, bulimia, or other feeding disorder; drug or alcohol withdrawal symptoms; substance abuse disorder (e.g., nicotine, cocaine, ethanol, opiates, or other drugs); 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; 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; sleep disorders induced by stress; stress- related illnesses; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; chronic fatigue syndrome; stress- induced headache; headache; cancer; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, senile

dementia of the Alzheimer's type, and multiinfarct dementia; 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; obesity and the metabolic syndrome; infertility; premature birth; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and heart related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, stress induced infections in humans and animals, 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., dependences on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia.

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

The therapeutically effective amounts of the compounds of the invention for treating the diseases or disorders described above in a warm-blooded animal can be determined in a variety of ways known to those of ordinary skill in the art, e.g., by administering various amounts of a particular agent to an animal afflicted with a particular condition and then determining the effect on the animal. Typically,

therapeutically effective amounts of a compound of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect. It will be understood, however, that the specific dose levels for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease. Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most CNS disorders, a dosage regimen of four-times daily or less is preferred. For the treatment of stress and depression, a dosage regimen of one or two-times daily is particularly preferred.

It will be appreciated that all combinations of specific and preferred embodiments discussed above and the examples discussed below are contemplated as being encompassed by the present invention, provided such combinations do not comprise inconsistent groupings. In addition, all examples described herein are for illustrative purposes, and are not intended to narrow the scope of the invention in any way.

Compounds of the invention can generally be prepared using the synthetic routes illustrated in the Schemes below. Starting materials can be prepared by procedures described in these schemes or by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in the schemes are as defined below or as in the claims.

The skilled artisan will appreciate that the introduction of certain substituents will create asymmetry in the compounds of Formula I. The present invention contemplates all enantiomers and mixtures of enantiomers and stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, including racemates. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral phase gas chromatography, chiral-phase high performance liquid chromatography, or crystallizing the compound as a chiral salt complex. Enantiomers and stereoisomers can

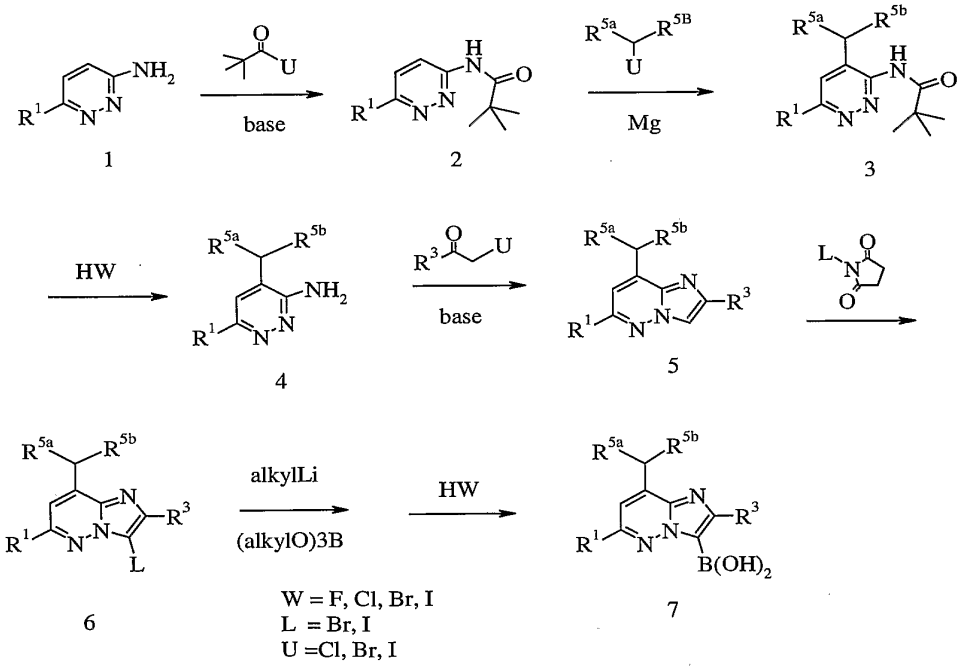
also be obtained from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

Pharmaceutically acceptable salts are contemplated to be within the scope of the present invention. The compounds of the present invention are bases and salts of such compounds may be formed with acids, for example, a salt with inorganic acid such as hydrochloric acid or a salt with organic acid such as trifluoroacetic acid.

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. These schemes, therefore, are not limited by the compounds listed nor by any particular substituents employed for illustrative purposes.

Scheme I

Synthesis of Imidazo[1,2-b]pyridazine fragment



R^1, R^3, R^{5a}, and R^{5b} are defined supra.

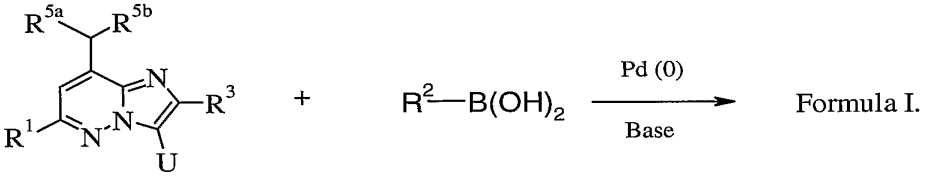
In Scheme I, a substituted 3-amino-pyridazine 1 is acylated with pivaloyl halide and a base, e.g., triethylamine in a polar aprotic solvent, e.g., methylene chloride at from

room temperature to the reflux to give amide 2. Amide 2 is treated with a Grignard reagent in diethylether or THF to give the 4-substituted amide 3. Amide 3 is hydrolyzed with aqueous HCl at from room temperature to 110 °C then neutralized to provide free amine 4. Amine 4 is treated with an alpha-halo ketone and base, e.g., sodium bicarbonate in 95% ethanol at from room temperature to 110 °C to give imidazopyridazine 5. Imidazopyridazine 5 is treated with a halogenating reagent e.g., N-iodo or N-bromosuccinimide in a polar aprotic solvent (e.g., acetonitrile) at from 0 °C to room temperature to give halide 6. Halide 6 undergoes halogen metal exchange with an alkyl lithium reagent, e.g., n-, sec-, or tert- butyllithium in diethylether or THF at from –78 °C to room temperature, followed by treatment with a trialkylborate, e.g., trimethylborate to give an intermediate boronic ester, which is hydrolyzed upon workup with aqueous HCl to provide boronic acid 7.

Scheme II

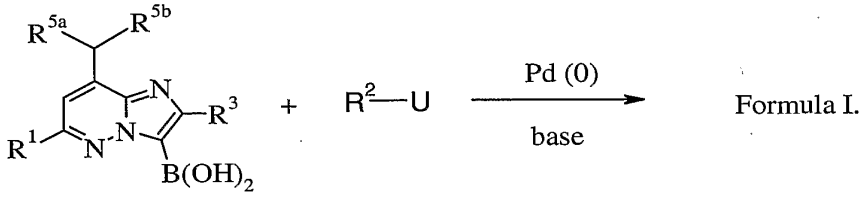
Synthesis of Compounds of Formula I by transition metal catalysis.

Equation 1.



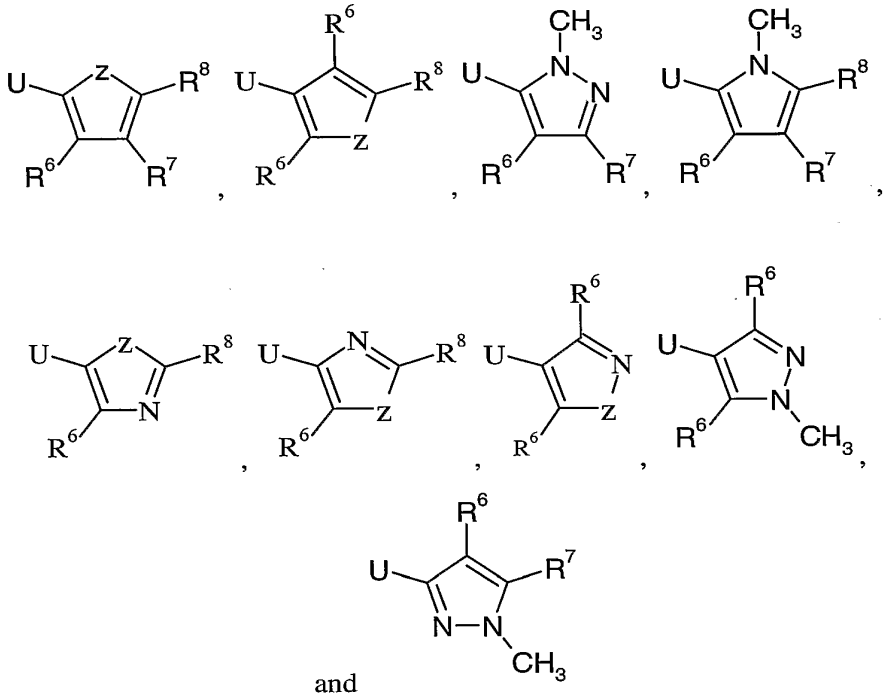
6 8

Equation 2.



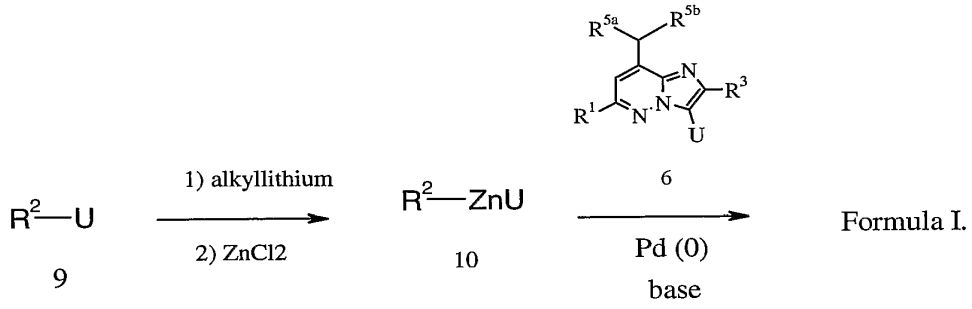
7 9

Where R^2-U is selected from the group consisting of:

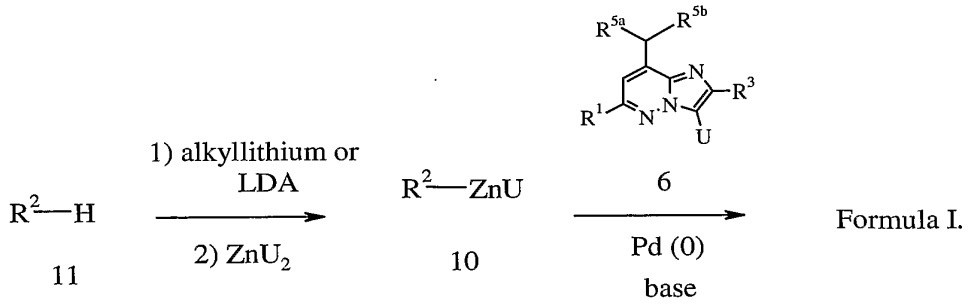


and

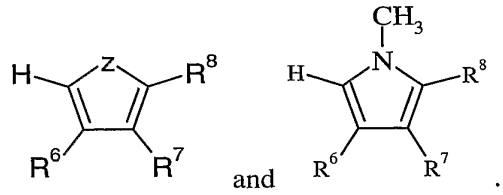
Equation 3.



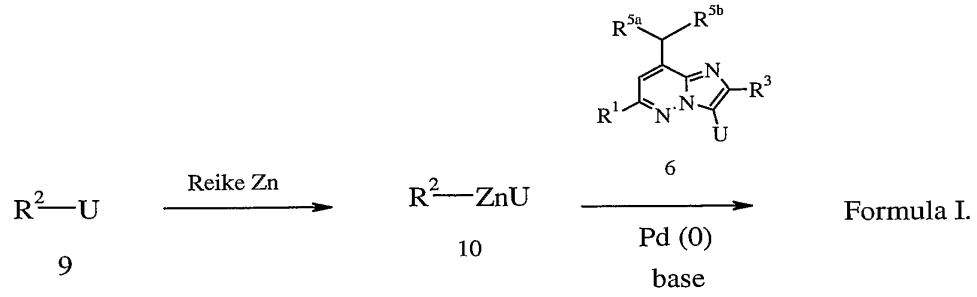
Equation 4.



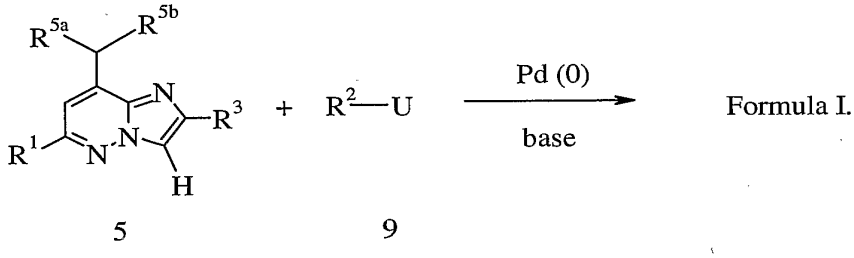
Where R^2-H is selected from the group consisting of:



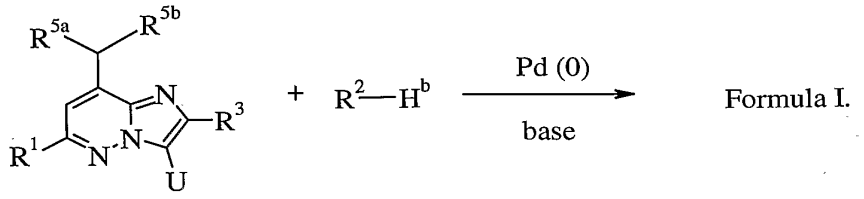
Equation 5.



Equation 6.



Equation 7.



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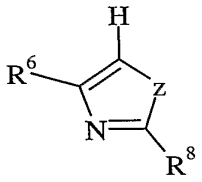
Where R^2-H^b is selected from:



R^1, R^2, R^3, R^{5a}, R^{5b} R^6, R^7, R^8, U, and z are defined supra.

In Scheme II equation 1, halide 6 can be used in a coupling reaction with a 5-membered ring heterocyclic boronic acid 8 in the presence of palladium catalysis, e.g., tetrakis-triphenylphosphine palladium (0) in a lower alkanol (methanol or n- or i-propanol)/DME mixture at from 70-120 °C to give compounds of formula I.

Alternately in equation 2, boronic acid 7 can be used in a coupling reaction with a 5 membered ring heterocyclic halide 9 and palladium catalysis, e.g., tetrakis-triphenylphosphine palladium (0) in a lower alkanol (methanol or n- or i-propanol)/DME mixture at from 70-120 °C to give a compound of formula I.

In equation 3, 5-membered ring heterocyclic halides 9 may undergo halogen-lithium exchange with, e.g., n-, sec- or tert-butyl lithium in THF or ether at –65 °C, followed by lithium-zinc exchange with $ZnCl_2$ in either diethylether or THF at temperatures up to room temperature. The *in situ* organozinc reagent 10 may then undergo coupling with halide 6 in the presence of palladium, e.g., $PdCl_2$(dppf) in THF at from 70-120°C to give a compound of formula I.

In equation 4, a 5-membered heterocyclic ring with a ring proton may be lithiated by either an alkyllithium, e.g., n-, sec- or tert-butyl lithium or lithium diisopropyl amide in THF or ether at –65 °C to room temperature followed by lithium-zinc exchange with

anhydrous zinc halide in either diethylether or THF to give an organozinc reagent 10 that is used as in equation 3 above. One skilled in the art will also appreciate that commercially available organozinc reagents 10 can be used directly as an organozinc coupling partner.

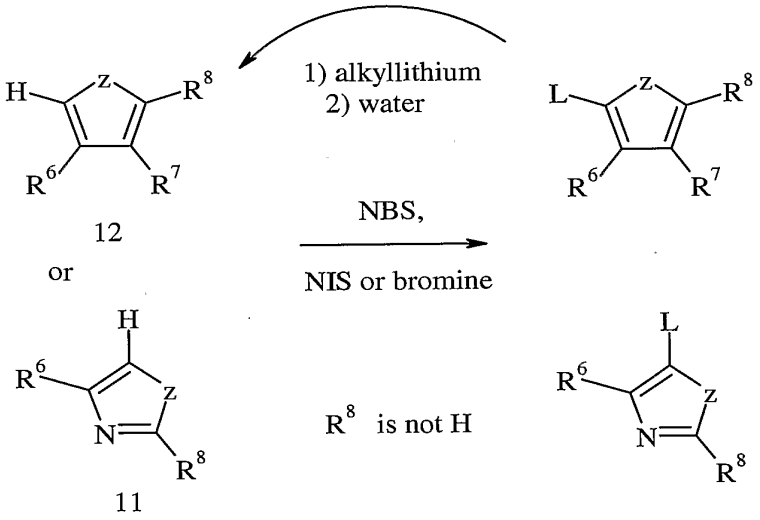
Furthermore from equation 5, it may be advantageous or convenient to use Reike Zn in THF to directly convert a 5-membered ring heterocyclic halide 9 to an organozinc reagent 10 for coupling with a halide 6.

In equation 6, a 5 membered heterocyclic halide 9 can be directly coupled with the imidazo[1,2-b]pyridazine intermediate 5 in the presence of palladium, e.g., $Pd_2(dba)_3$, $PdCl_2$, Palladium acetate/TDBPP, or tetrakis-triphenylphosphine palladium (0) in DMF, THF, or NMP solvent from 70-120°C to give a compound of formula I.

Alternately, from equation 7, the imidazo[1,2-b]pyridazine halide 6 may be directly coupled with a 5 membered heterocycle 11 in the presence of palladium, e.g., $Pd_2(dba)_3$, $PdCl_2$ or Palladium acetate/TDBPP in DMF, THF, or NMP solvent from 70-120 °C to give a compound of formula I.

Scheme III

Synthesis of Substituted 5 Membered Heterocyclic Halides



R^6, R^7, R^8, L, and z are defined supra.

Several 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 may be prepared by methods well know to the skilled artisan. From Scheme III, they may also be prepared by halogenation, e.g., with bromine, NBS or NIS. Furthermore, some of the intermediates 11 and 12 may be prepared by lithium halogen exchange followed by water quench.

Compounds of Formula I as intermediates in the preparation of other compounds of Formula I include the addition of aryllithium reagents (generated by the methods of equations 3 and 4 in Scheme II) to carbonyl compounds, e.g., aldehydes, ketones, esters, and Weinreb amides. The resulting carbinols or carbonyl compounds are further elaborated by halogenation under acidic conditions and by a second aryllithium addition, respectively.

Abbreviations

TBDMSCl or TBDMSiCl – tert-butyl-dimethylsilyl chloride

MS (ES) – Electrospray Mass spectrum

THF – tetrahydrofuran

DMSO – Dimethylsulfoxide

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

RBSN – round bottom single neck flask

SiO2 – silica gel

EtOAc, AcOEt – ethylacetate

GFF - glass microfiber filter

HPLC – high pressure liquid chromatography on silica gel

ISCO – ISCO brand low pressure liquid chromatography on silica gel

AcCl – acetyl chloride

LDA – lithium diisopropylamine

KOAc – Potassium Acetate

TBABr – Tetrabutyl ammonium bromide

NMP – N-Methylpyrrolidinone

TDBPP – Tris (2,4-di-*t*-butylphenyl) phosphite.

Pd_2dba_3 – Tris(dibenzylideneacetone)dipalladium

$PdCl_2(dppf)$ – Dichloro(diphenylphosphinoferrocene)palladium

Tetrakis – tetrakis-(triphenylphosphine)-palladium

Dppf - 1,1'-bis(diphenylphosphino)ferrocene)

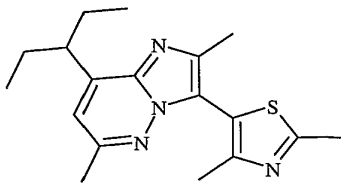
r.t., RT – room temperature

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 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. Examples 1-255 provide exemplary compounds and illustrate the preparation thereof. Examples A-D illustrate 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.

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-pyridizin-3-ylamine.

3-Chloro-6-methylpyridazine (25.0g, 0.229 moles) is dissolve in 250 mL of NH_4OH and heated to 170 °C in a sealed container for 24 hours. The solvents are evaporated. The residue is triturated in methylene chloride, and a solid is filtered. This trituration procedure is repeated with the filtrate four times. The filtered solids are combined and dried in a vacuum oven overnight to obtain the title compound as an off-white solid 4.32 g (0.040 moles, 20%). ^{1}H-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).

B. 2,2-Dimethyl-N-(6-methyl-pyridazine-3-yl)-propionamide.

Method 1: To a dry flask is added 7.12 g (0.065 mole) of 6-methyl-pyridizin-3-ylamine in 170 ml dry methylene chloride. Next, 14.5 ml of triethylamine is added and the reaction is cooled to 0 °C. Pivaloyl chloride (2.7 ml, 1.2 eq) is carefully added, and the reaction mixture is stir 10 minutes, removed from the bath, and stirred 4 hours more. Dichloromethane (200 mL) is added, and the reaction mixture is washed 3 times with saturated aqueous sodium bicarbonate, then 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 a hexane:ethyl acetate gradient giving the title compound as a white solid weighing 1.51 g (7.8 mmoles, 42.7%). ^{1}H-NMR (DMSO-d_6), 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: To a dry pressure tube is added 200 mg (1.56 mol) of 3-chloro-5-methylpyridazine, 190 mg (1.87 mmol) of trimethylacetamide, 14.6 mg (0.023 mmol) of rac-2,2'-bis(diphenylphosphine)-1,1'-binaphthyl , tris(dibenzylideneacetone)-dipalladium (0) , 762.4 mg (2.34 mmol) of cesium carbonate and 1.5 ml dry tetrahydrofuran. The pressure tube is purged with nitrogen and sealed. The reaction is heated to 100 °C overnight. The reaction is then cooled, diluted with dichloromethane, and filtered through celite. Solvents are evaporated and the crude product is purified via silica gel chromatography using a ethyl acetate:hexane gradient to obtain 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.

Activated magnesium powder (19.2 g, 0.792 moles) is added to a dry 3 L flask fitted with a condensor and a drop funnel. The entire apparatus is heated with a gun dry under vacuum and allowed to cool. Enough ether is added to cover the magnesium. 3-Bromopentane (100 g, 0.662 mmol) is added to the addition funnel in 175 ml of diethyl ether. A 1/3 of the bromopentane solution is added to the magnesium and the reaction mixture is stirred under nitrogen until bubbling occurs. Then, the rest is dripped in at such a rate that the bubbling continues gently. The reaction is stirred for 30 minutes after bubbling ceases. Next, 2,2-dimethyl-*N*-(6-methyl-pyridazine-3-yl)-propionamide (21.3 g, 0.110 mmol) dissolved in 225 ml of dry THF is added dropwise. The reaction mixture is stirred for 1 hour. Saturated sodium tartrate (1 L) is carefully added, and the reaction is stirred for 30 minutes. The reaction mixture is transferred to a larger flask, 2 L of ethyl acetate is added, and the reaction is stirred 1 hour more. The layers are separate and the aqueous layer is extracted several times with ethyl acetate. The organic extracts are combined, and the solvents are evaporated. The residue is taken up 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 aqueous solution of sodium sulfite and then with water. The organic layer is dried over sodium sulfate, filtered, and evaporated to red oil. The crude product is purified via silica gel chromatography using a hexanes:ethyl acetate gradient. The product fractions are combined and evaporated. The residue is triturated in ethyl acetate and a light tan solid is filtered to obtain 12.0 g (45.6 mmol, 41 %) of the title compound. ^{1}H-NMR (DMSO-d_6), 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); 1.38-1.43(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 of concentrated hydrochloric acid. The reaction mixture is heated to 95 °C in a sealed flask for 2 hours. The reaction is worked up by pouring over ice and extracting with ethyl acetate three times. The organic layer is discarded, and the pH of the aqueous layer is adjusted using 2 N sodium hydroxide. The basic solution is extracted with ethyl acetate five times. The organic extracts are

combined, dried over magnesium sulfate, filtered, and evaporated to obtain 6.68 g (37 mmol, 81%) of the title compound as a brownish oil. ^{1}H-NMR (DMSO-d_6), δ 6.95 (s, 1H); 5.89 (s, br, 2H); 2.52-2.56 (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 (0.415 ml, 5.22 mL) and 20 mL of ethanol are heated in the microwave at 110 °C for 35 minutes. Sodium bicarbonate (1.2 g, 14.2 mmol) is added, and the reaction mixture is heated in an oil bath at 100 °C overnight. The solvent is evaporate and the residue is taken up in ethyl acetate and washed three times with brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to a brown 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%). ^{1}H-NMR (DMSO-d_6), δ 7.34 (s, 1H); 6.84 (s, 1H); 2.85-3.10 (m, 1H); 2.43 (s, 3H); 2.32 (s, 3H); 1.70-1.80 (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 moles) and 50 mL of dry acetonitrile are added to a nitrogen purged flask and are cooled to 0 °C. *NIS* (5.54 g,0.025 moles) in 90 mL of dry acetonitrile is added. The bath is allowed to come to room temperature, and the reaction to stir overnight. The solvents are evaporated. The residue is taken up in ethyl acetate, washed two times with 50% aqueous solution of sodium thiosulfate and with brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to a residue again. The crude product is triturated in a small amount of acetonitrile, and a solid is filter off. The trituration is repeated several times to obtain the title compound as a light tan solid weighing 7.29 g (0.021 moles, 91%). ^{1}H-NMR (DMSO-d_6), 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*]pyridazine-3-yl boronic acid.

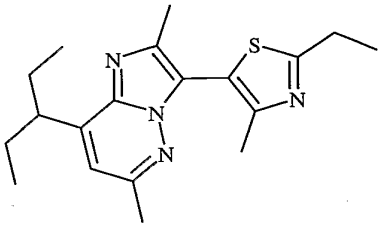
In an oven dried nitrogen purged 3 neck 50mL round bottom flask, 1.00g (2.91 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine in 60mL of dry THF is cooled to -78°C. 4.12mL (7.00mmol) of 1.7 M tert-butyllithium in hexanes is added and reaction is stirred at -78 °C for 1 hour. 0.818mL (7.30mmol) of trimethyl borate is added and reaction is followed by MS and TLC (1:1 Hexane:EA) Indication of product is observed by mass spectrum. The reaction is allowed to stir for an additional hour, quenched with 1 N hydrochloric acid, and diluted with ethyl acetate. The organic layer is separated, and the aqueous layer is extracted three times with 100 mL of ethyl acetate. The extracts are combined, dried over $MgSO_4$, filtered, and concentrated. The reaction residue is triturated in hexanes and a solid is filter 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.

To a microwave pressure tube is added 0.340g (1.30mmol) of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine-3-yl boronic acid, 0.100g (0.521mmol) of 5-bromo-2,4-dimethylthiazole, 0.361g (0.313mmol) of Pd(PPh3)4, 0.650mL (1.30mmol) of 2 M aqueous Na2CO3, and 2mL 7:3:2 DME:H2O:EtOH, and the mixture is heated at 160 °C for 40min. Reaction is checked by MS which indicates product present. The reaction mixture is partitioned between 75mL of ethyl acetate and 75mL of water. The layers are separated and the aqueous is extracted 3X50mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using hexanes/ethyl acetate as a solvent system. The product containing fractions are combined to obtain 0.100g of the product, 58% yield. MS, ES+ = 329.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.974 (s, 1H); 3.085-3.052 (m, 1H); 2.665 (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-methylthiazole.

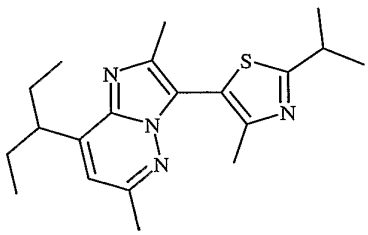
In an oven dried, N_2 purged, 50 mL round bottom flask, 1.00 g (7.86 mmol) of 2-ethyl-4-methylthiazole is reacted with 0.487 mL (9.43 mmol) of bromine in 7mL of acetic acid at room temperature. Reaction is checked by MS after 2 hours. The reaction mixture is partitioned between 50 mL H_2O and 25 mL of CH_2Cl_2. The layers are separated and the aqueous is extracted 3X25mL of CH_2Cl_2. The organics are combined and washed 1X25mL 1N $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated under vacuum to give 1.38g of the title compound, 85% yield. MS, ES+ = 206.0 (M+1); ^{1}H-NMR (DMSO-d6) = 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, 5-bromo-2-ethyl-4-methylthiazole produces the title product in 27% yield. MS, ES+ = 343.2 (M+1); ^{1}H-NMR (DMSO-d6) = 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-methylthiazole.

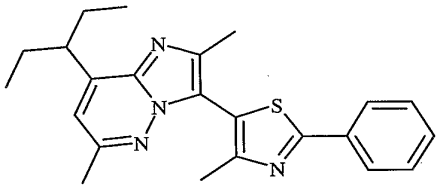
Using a procedure similar to Example 2A, 2-isopropyl-4-methylthiazole produces the title product in 90% yield. MS, ES+ = 220.0 (M+1); ^{1}H-NMR (DMSO-d6) = 3.210-3.175 (m, 1H); 2.257 (s, 3H); 1.264-1.248 (d, 6H) ppm.

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, 5-bromo-2-isopropyl-4-methylthiazole produces the title product in 29% yield. MS, ES+ = 357.2 (M+1); ^{1}H-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-methy-2-phenylthiazole.

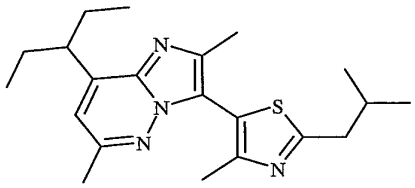
Using a procedure similar to Example 2A, 4-methyl-2-phenylthiazole produces the title product in 90% yield. MS, ES+ = 256.0 (M+1); ^{1}H-NMR (DMSO-d6) = 7.900-7.867 (m, 2H); 7.538-7.512 (m, 3H); 2.407 (s, 3H) ppm.

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, 5-bromo-4-methyl-2-phenylthiazole produces the title product in 24% yield. MS, ES+ = 391.3 (M+1); ^{1}H-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); 2.496 (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-methy-2-(2-methyl)propylthiazole.

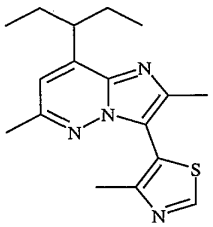
Using a procedure similar to Example 2A, 4-methyl-2-(2-methyl)propylthiazole produces the title product in 96% yield. MS, ES+ = 234.1 (M+1); ^{1}H-NMR (DMSO-d6) = 2.744 (m, 2H); 2.259 (s, 3H); 1.895-2.000 (m, 1H); 0.905-0.888 (m, 6H) ppm.

B. 8-(1-Ethyl-propyl)-3-(4-methyl-2-(2-methyl)propyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-4-methyl-2-(2-methyl)propylthiazole produces the title product in 7% yield. MS, ES+ = 371.3 (M+1); ^{1}H-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); 2.107-2.073 (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.

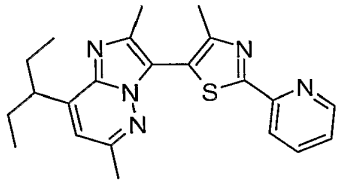


3.00 g of 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (8.74 mmol), 4.32 g of 4-methyl-2*H*-thiazole (43.6 mmol), 453 mg of triphenylphosphine (1.73 mmol) and 5.85 g of cesium carbonate (18.0 mmol) are placed into the sealed tube with

20 ml of DMF and N2 gas is bubbled in for 40 min. 39 mg of Pd2dba3 (0.43 mmol) is added and the tube is sealed and heated at 130°C overnight. The cooled reaction mixture is filtered and applied onto silica-gel column (Hexane → Hexane : AcOEt = 3: 1) to give 2.12 g of the title compound (77%).^{1}H-NMR (DMSO-d6) δ 9.215 (s, 1H); 6.993 (s, 1H); 3.079 (m, 1H); 2.480 (s, 3H); 2.439 (s, 3H); 2.302 (s, 3H); 1.824-1.751 (m, 4H); 0.780-0.743 (m, 6H) ppm. MS, ES+ = 315.2.

Example 7.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-2-yl-thiazol-5-yl)-imidazo[1,2-*b*]pyridazine.



A. 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

In an oven dried, N2 purged, 15mL round bottom flask, 0.028 g (0.089 mmol) of 8-(1-ethyl-propyl)-3-[4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine. in 1.5mL of dry CH_2Cl_2 is cooled to 0 C. 0.019 g (0.107 mmol) of NBS is added and reaction is stirred overnight allowing bath to come to room temperature. Reaction mixture is directly purified by chromatography using hexane/ethyl acetate as solvent system. The product containing fractions are combined to obtain 0.012 g, 34% yield. MS, ES+ = 395.1 (M+1); ^{1}H-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.

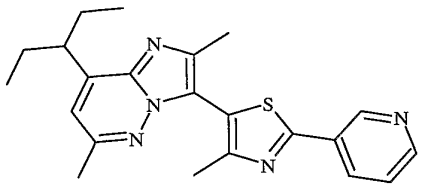
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-2-yl-thiazol-5-yl)-imidazo[1,2-*b*]pyridazine.

A mixture of 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-pyridinezinc bromide (0.5 M in THF, 2.1 mL, 4 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) and THF (3 mL) is heated at 80 °C for 18 hours. Ethyl acetate (20 mL) is added. 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 hexanes and ethyl acetate as eluent to produce the title compound 325 mg (86%). ^{1}H-NMR ($CDCl_3$), δ 9.55 (m,1H); 8.10 (m, 1H); 7.73 (m,1H); 7.26 (m,1H); 6.58 (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 8.

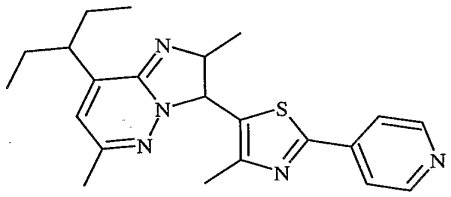
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-pyridyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a microwave pressure tube is added 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, 0.066g (0.534 mmol) of pyridine-3-boronic acid, 0.103 g (0.089 mmol) of Pd(PPh3)4, 0.267mL (0.534 mmol) of 2 M aqueous Na2CO3, and 1mL 7:3:2 DME:H2O:EtOH, and the mixture is heated at 160 °C for 60 min. The reaction mixture is partitioned between 25mL of ethyl acetate and 25 mL of water. The layers are separated and the aqueous is extracted 3X 25 mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using hexanes/Ethyl acetate as a solvent system. The product containing fractions are combined to obtain 0.045 g of the product, 64% yield. MS, ES+ = 392.2 (M+1); ^{1}HNMR (DMSO-d6) δ 9.18 (s, 1H); 8.65 (m, 1H); 8.34 (d, 1H); 7.60 (m, 1H); 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.

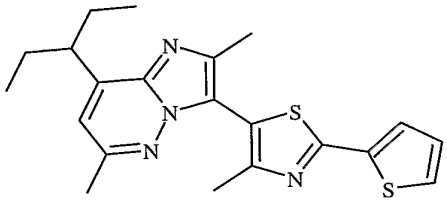
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-pyridyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, pyridine-4-boronic acid produces the title compound in 10% yield. MS, ES+ = 392.3 (M+1); ^{1}HNMR (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.

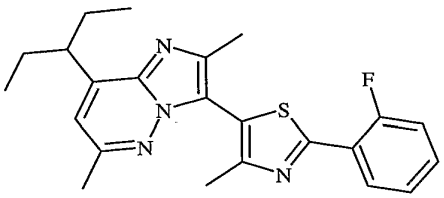
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(thiophene-2-yl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, thiophene-2-boronic acid produces the title compound in 89% yield. MS, ES+ = 397.1 (M+1); ^{1}H-NMR (DMSO-d6) = 7.81-7.79 (d, 1H); 7.78-7.77 (d, 1H); 7.21-7.20 (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.

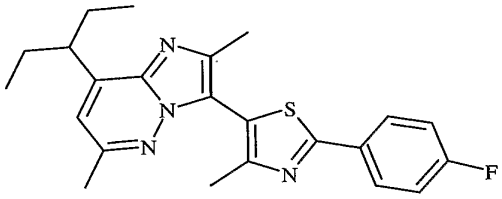
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 2-fluorophenyl boronic acid produces the title compound in 82% yield. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.32-8.28 (m, 1H); 7.60-7.58 (m, 1H); 7.57-7.41 (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.

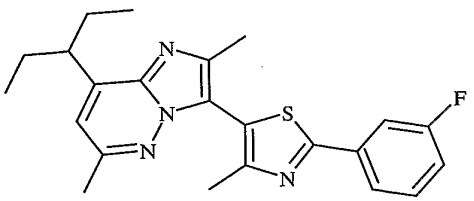
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 4-fluorophenyl boronic acid produces the title compound in 63% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.06-8.03 (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.

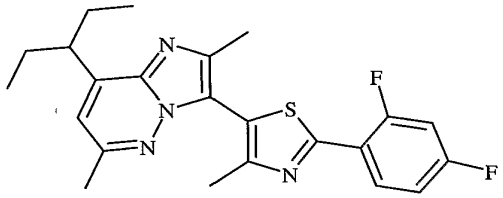
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 3-fluorophenyl boronic acid produces the title compound in 77% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 409.2 (M+1); ^{1}H-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); 3.15-3.111 (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

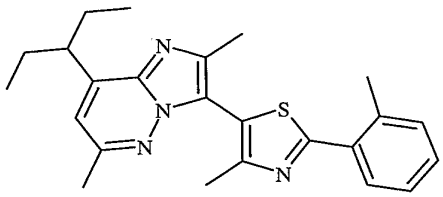
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 2,4-difluorophenyl boronic acid produces the title compound in 76% yield. MS, ES+ = 427.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.370-8.310 (m, 1H); 7.586-7.540 (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.

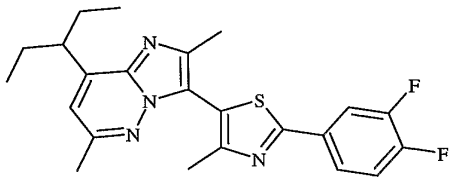


Using a procedure similar to Example 8, o-tolyl boronic acid produces the title compound in 87% yield where the crude mixture is purified by silica gel chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 405.2 (M+1); ^{1}H-

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); 2.502 (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.

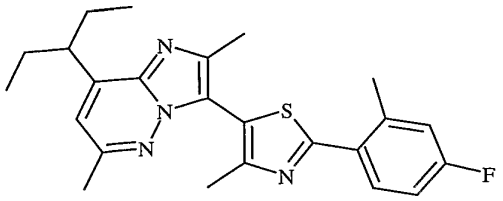
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 3,4-difluorophenyl boronic acid produces the title compound in 74% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 427.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.07-8.02 (m, 1H); 7.849 (s, 1H); 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) 1.905-1.779 (m, 4H); 0.826-0.790 (m, 6H) ppm.

Example 17.

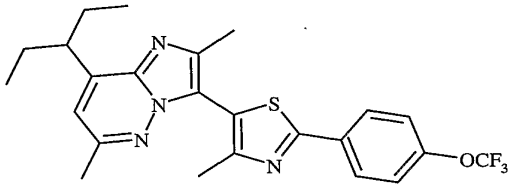
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluoro-2-methylphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 4-fluoro-2-methylphenyl boronic acid produces the title compound 0.040g (37% yield). MS, ES+ = 423.2 (M+1); ^{1}H-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.

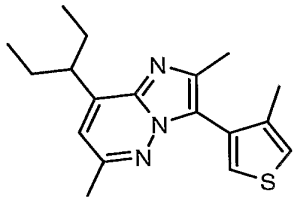
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-trifluoromethoxyphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a microwave pressure tube is added 0.100g (0.254mmol) of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 0.157g (0.762mmol) of 4-(trifluoromethoxy)benzene boronic acid, 0.147g (0.127mmol) of Pd(PPh3)4, 0.381mL (0.762mmol) of 2 M aqueous sodium carbonate, and 2mL Ethanol. The reaction mixture is heated in the microwave at 160°C for up to 1 hour. The reaction mixture is partitioned between 50 mL of ethyl acetate and 50 mL of water. The layers are separated and the aqueous is extracted 3X50mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. The product containing fractions are combined to obtain 0.085g of the product, 70% yield. MS, ES+ = 475.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.134-8.112 (d, 2H); 7.553-7.532 (d, 2H); 7.059 (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.

To a 250 mL round bottom flask is added 3-bromo-4-methyl-thiophene (5.00 g, 28.24 mmol), bis(pinacolato)diboron (7.89 g, 31.06 mmol) and KOAc (8.32 g, 84.72 mmol) in DMSO (85 mL). The mixture is degassed by bubbling N_2 for 5 min, $PdCl_2(dppf)_2 \bullet CH_2Cl_2$ (1.15 g, 1.42 mmol) is added and the reaction mixture is heated to and stirred at 85 °C overnight. The reaction is cooled to rt, and diluted with EtOAc (400 mL), washed with H_2O (3 x 300 mL); dried with $MgSO_4$, filtered and concentrated. Purification of the crude material by chromatography to give the title compound (3.69 g, 16.5 mmol, 58%). ES-MS (m/z): calcd for $C_{11}H_{17}BO_2S$ (M^+): 224.1; found: 224.9.

B. 4-Methyl 3-thiophene boronic acid.

A solution of 4,4,5,5-tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane (3.69 g, 16.47 mmol) in acetone (30 mL) is treated with H_2O (30 mL), followed by $NaIO_4$ (7.05 g, 32.95 mmol). The resulting mixture is stirred at rt overnight. The organic solvent is removed in vacuo. The residue is diluted with H_2O (50 mL), extracted with EtOAc ((2 x 100 mL). The organic extracts are combined, dried with Na_2SO_4, filtered and concentrated. Purification of the crude material by chromatography gives the title compound (0.82 g, 5.78 mmol, 35%). ^1H NMR ($CDCl_3$): 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 for $C_5H_7BO_2S$ $(M-H)^-$: 141.0; found: 141.1.

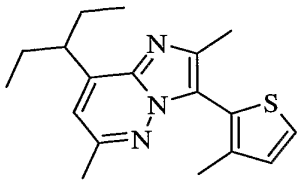
C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

To a 100 mL round bottom flask containing 4-methyl 3-thiophene boronic acid (0.27 g, 1.91 mmol), and 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.65 g, 1.91 mmol) in 20 mL of a stock solution (DME:H_2O:EtOH = 7:3:2) is added 2 M Na_2CO_3 (1.9 mL). The resulting mixture is degassed by bubbling N_2 for 5 min. Then $Pd(PPh_3)_4$ (0.11 g, 0.096 mmol) is added. The reaction mixture is refluxed overnight. The reaction is diluted with H_2O (20 mL); extracted with EtOAc (3 x 30 mL); dried (Na_2SO_4), filtered and purification of the crude material by chromatography gives the title compound (0.52 g, 1.66 mmol, 87%). ^1H NMR ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz,

6H), 1.75-1.90 (m, 4H), 2.13 (d, J = 0.8 Hz, 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), 7.34 (d, J = 3.1 Hz, 1H). ES-MS (m/z): calcd for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.5; found: 314.2.

Example 20.

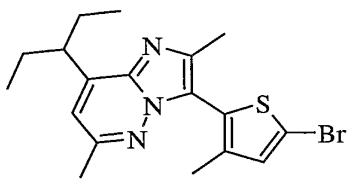
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To mixture of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (12.0 g, 34.96 mmol) and $PdCl_2$(dppf) (1.28 g, 1.75 mmol) is added a 0.5 M solution of 3-methyl-2-thienylzinc bromide in THF (100 mL, 50.0 mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (500 mL), washed with 10% citric acid (500 mL), water (400 mL), brine (400 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (10%-20% EtOAc/hexane gradient) furnish the title compound (8.83 g, 28.17 mmol, 81%). ^{1}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. for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.6; found: 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.

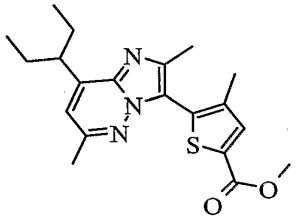


To a solution of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (8.83 g, 28.17 mmol) and CH_2Cl_2 (90 mL) is added NBS (5.26

g, 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 furnish the title compound (10.5 g, 26.76 mmol, 95%). ^{1}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), 3.26-3.36 (m, 1H), 6.68 (s, 1H), 6.98 (d, J = 4.9 Hz, 1H) ppm. LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.6; found: 392.1, 394.1.

Example 22.

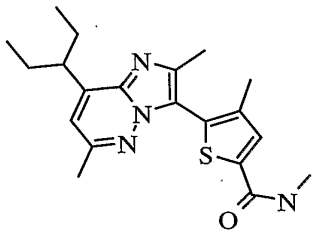
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methyl ester.



A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.00 g, 2.66 mmol) in CH_3OH (12 mL), DMSO (18 mL), Et_3N (2.0 mL) with $Pd(OAc)_2$ (0.12 g, 0.538 mmol), dppf (0.937 g, 1.69 mmol) is reacted at CO atmosphere (100 psi) at 80 °C for 24 h. The reaction mixture is diluted with EtOAc (200 mL), washed with 0.1 M HCl (2 x 50 mL), brine (50 mL); dried with Na_2SO_4; filtered through silica gel and eluted with excess EtOAc. Purification of the crude material by chromatography gives the title compound (0.79 g, 2.12 mmol, 80%). ^{1}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 for $C_{20}H_{25}N_3O_2S$ $(M+H)^+$: 372.5; found: 372.2.

Example 23.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methylamide.



A. 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid.

A solution of (1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methyl ester (0.78 g, 2.10 mmol) in CH_3OH (10 mL) is treated with 5.0 M NaOH (2.1 mL, 10.5 mmol). The resulting reaction mixture is refluxed for 4 h. Organic solvent is removed in vacuo; the aqueous residue is acidified by the addition of 2.0 M HCl to pH 5~6; it is then extracted with EtOAc (3 x 50 mL); dried (Na_2SO_4); filtered and concentration to give the title compound (0.74 g, 2.07 mmol, 98%). ^{1}H NMR (DMSO-d6): δ 0.79 (t, J = 7.6 Hz, 6H), 1.75-1.86 (m, 4H), 2.06 (s, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 3.06-3.14 (m, 1H), 7.01 (s, 1H), 7.68 (s, 1H), 13.1 (bs, 1H). ES-MS (m/z): calcd for $C_{19}H_{23}N_3O_2S$ $(M+H)^+$: 358.5; found: 358.2.

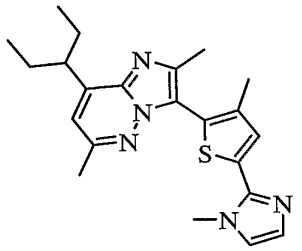
B. 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methylamide.

5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid (0.17 g, 0.47 mmol) is reacted with 2.0 M oxalyl chloride in CH_2Cl_2 (3.0 mL) at rt for 1h. The excess reagent and solvent are removed in vacuo. The residue is dissolved in CH_2Cl_2 (3mL), cooled to 0 °C and treated with 2.0 M methyl amine in THF (3 mL). The reaction is stirred at 0 °C for 10 min and rt for 30min. It is diluted with EtOAc (50 mL), washed with H_2O (15 mL0, 0.1 M NaOH (2 x 30 mL); dried (Na_2SO_4); filtered and concentrated. Purification of the crude material by chromatography to give the title compound (0.91g, 0.25 mmol, 53%). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 6H), 1.75-1.91 (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 for $C_{20}H_{26}N_4OS$ $(M+H)^+$: 371.5; found: 371.2.

Example 24.

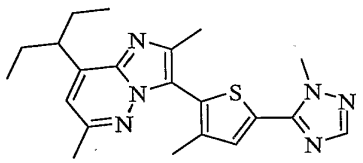
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-imidazol-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo-[*1,2-b*]pyridazine (0.98 g, 2.51 mmol) and 1-methyl-*1H*-imidazole (0.2 mL), $Pd(OAc)_2$ (34 mg, 0.15 mmol), PPh_3 (79 mg, 0.299 mmol), Cs_2CO_3 (1.95 g, 6.0 mmol) in DMF (50 mL) is stirred under N_2 at 130-140°C overnight. The reaction mixture is cooled, diluted with EtOAc (300 mL), washed with H_2O (3 x 100 mL); dried (Na_2SO_4); filtered and concentrated. Purification of the resulting crude material by chromatography yields the title compound (0.51 g, 1.29 mmol, 51%). ^1H 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 for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.6; found: 394.3.

Example 25.

Preparation of 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.

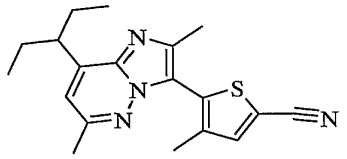


To a –78 °C solution of 1-methyl-1,2,4-triazole (0.15 mL, 2.04 mmol) and THF (3 mL) is added a 1.34 M solution of n-Bu-Li in hexanes (1.60 mL, 2.14 mmol) over 20

minutes, then stirred at –78 °C for 1.5 hours. A 0.5 M solution of $ZnCl_2$ in THF (4.28 mL, 2.14 mmol) is added and the solution warmed 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 $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and the solution heated at 65 °C overnight diluted with CH_2Cl_2 (30 mL). The organic layer is washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (20%-60% EtOAc/hexane gradient). The residue is dissolved in Et_2O, treated with Darco®-60 for 15 minutes, dried with Na_2SO_4, and filtered to furnish the title compound (0.24 g, 0.61 mmol, 60%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.20 (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. for $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.6; found: 395.2.

Example 26.

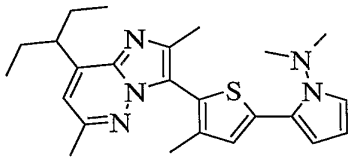
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carbonitrile.



A solution of 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) is degassed with nitrogen for 15 minutes. $Pd(PPh_3)_4$ (0.74 g, 0.064 mmol) and the solution heated at 100 °C overnight. The solution is diluted with EtOAc (50 mL), washed with 2 M NH_4OH (2 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO column chromatography (15% - 20% EtOAc/hexane gradient) furnish the title compound (0.39 g, 1.15 mmol, 91%). ^{1}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), 3.26-3.34 (m, 1H), 6.72 (s, 1H), 7.53 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{22}N_4S$ $(M+H)^+$: 339.6; found: 339.2.

Example 27.

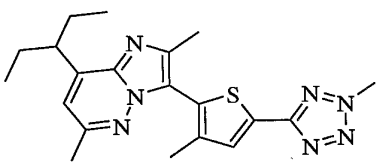
Preparation of (2-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyrrol-1-yl)-dimethyl-amine.



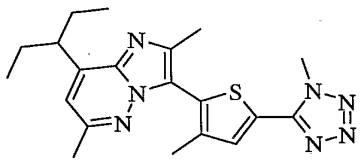
To a 0 °C solution 1-(dimethylamino)-pyrrole (0.24 mL, 2.04 mmol) and THF (4 mL) is added 1.24 M *n*-BuLi (1.73 mL, 2.14 mmol). The solution is warmed to ambient temperature and stirred for two hours. 0.5 M $ZnCl_2$ (4.28 mL, 2.14 mmol) is added and the solution is stirred for one hour. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and the solution is heated at 65 °C overnight. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% -20% EtOAc gradient) furnish the title compound (0.41 g, 0.97 mmol, 95%). ^1H NMR ($CDCl_3$) 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. for $C_{24}H_{31}N_5S$ $(M+H)^+$: 422.2; found: 422.4.

Example 28 and 29.

Preparation of 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.



Ex 28.



Ex. 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.

To a solution of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carbonitrile (0.25 g, 0.74 mmol) and DMF (2.5 mL) is added Et_3N•HCl (0.31 g, 2.22 mmol) and NaN_3 (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 X 15 mL), the combined organic layers are washed with 0.1 M HCl (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is recrystalized from acetonitrile furnish the title compound (0.14 g, 0.37 mmol, 50%). ^{1}H NMR ($CDCl_3$), 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), 6.83 (s, 1H), 7.84 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{23}N_7S$ $(M+H)^+$: 382.6; found: 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.

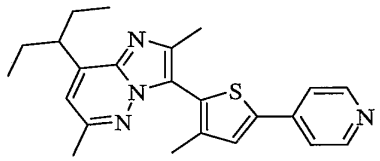
To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.14 g, 0.35 mmol) and THF (3 mL) is added Et_3N (0.1 mL, 0.71 mmol) and MeI (0.024 mL, 0.39 mmol). The solution is stirred overnight, diluted with EtOAc (20 mL), washed with water (15 mL), 0.1 M HCl (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%- 40% EtOAc/hexane gradient) furnish Ex. 28 (0.71 g, 0.18 mmol, 51%), and Ex. 29 (0.031 g, 0.078 mmol, 22%).

Ex. 28: ^{1}H NMR ($CDCl_3$), 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. for $C_{20}H_{25}N_7S$ $(M+H)^+$: 396.6; found: 396.3.

Ex. 29: ^{1}H NMR ($CDCl_3$), 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. for $C_{20}H_{25}N_7S$ $(M+H)^+$: 396.6; found: 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.

To a -78 °C solution of 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 1.30 M *n*-Bu-Li (2.47 mL, 3.21 mmol) drop wise. The solution is stirred at –78 °C for one hour. $B(OMe)_3$ (0.38 mL, 3.65 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hours. 1 M HCl is added and the solution stirred for 10 minutes extracted with CH_2Cl_2 (2 X 30 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.47 g, 1.32 mmol, 43%). ^1H NMR ($CDCl_3$), 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): calcd. for $C_{18}H_{24}BN_3O_2S$ $(M+H)^+$: 358.4; found: 358.2.

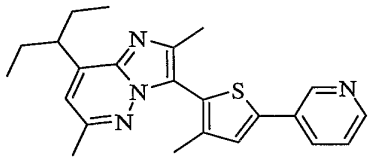
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

A solution of 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 2 M Na_2CO_3 (0.87 mL, 1.75 mmol) and *n*-PrOH (2.5 mL) is degassed with nitrogen for 10 minutes. $Pd(PPh_3)_4$ (0.040 g, 0.035 mmol) is added and the solution heated at 85 °C overnight. The solution is diluted with CH_2Cl_2 (40 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 column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.16 g, 0.41 mmol, 59%). ^1H NMR ($CDCl_3$), 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. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2 found: 391.2.

Example 31.

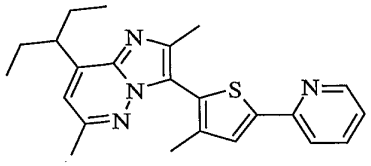
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-3-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 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 THF (5 mL) is added 1.34 M *n*-Bu-Li (1.0 mL, 1.34 mmol). The solution is stirred for at -78 °C for 30 minutes and 0.5 M $ZnCl_2$ in THF (2.7 mL, 1.34 mmol) is added and the solution warmed to ambient temperature. After 30 minutes 3-bromopyridine (0.15 mL, 1.53 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) is added and the solution heated at 65 °C overnight. The solution is diluted with CH_2Cl_2 (40 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) concentrated and re-dissolved in Et_2O. The solution is treated with Darco®-60 for 15 minutes, dried over Na_2SO_4, and filtered thru celite® furnish the title compound (0.26 g, 0.67 mmol, 52%). ^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), 6.68 (s, 1H), 7.26-7.32 (m, 2H), 7.86 (dt, J = 7.9, 1.8 Hz, 1H), 850 (d, J = 3.2 Hz, 1H), 8.89 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; found: 391.2.

Example 32.

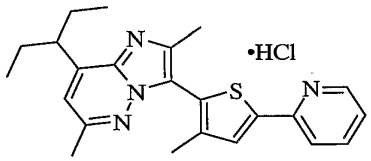
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a mixture of 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) (0.047 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 is stirred at 65 °C overnight, diluted with EtOAc (50 mL), washed with 10% citric acid (50 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.45 g, 1.15 mmol, 89%). ^{1}H NMR ($CDCl_3$), 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. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; found: 391.2.

Example 33.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine hydrochloride.

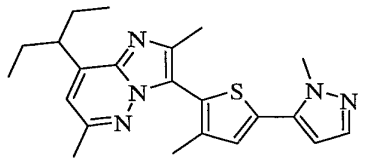


To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (0.15 g, 38 mmol) and MeOH (2 mL) is added AcCl (0.028 mL, 0.39 mmol). After one hour the solution is concentrated and the residue recrystalized from EtOAc/ hexane furnish the title compound (0.11 g, 0.26 mmol, 69%). ^{1}H 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-

7.7.82 (m, 2H), 8.60 (d, J = 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}ClN_5S$ $(M+H)^+$: 428.1; found: 391.2.

Example 34.

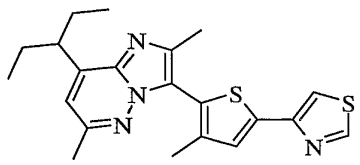
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2*H*-pyrazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 1-methylpyrazole (0.17 g, 2.04 mmol), 1.56 M *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 $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.35 g, 0.89 mmol, 88%). ^{1}H 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), 4.05 (s, 3H), 6.42 (d, J = 1.8 Hz, 1H), 6.68 (s, 1H), 7.08 (s, 1H), 7.46 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.7; found: 394.2.

Example 35.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-thiazol-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

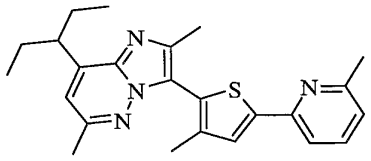


Using a procedure similar to Example 31, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.40 g, 1.02 mmol), 1.34 M *n*-Bu-Li (0.8 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 4-bromo-thiazole (0.20 mL, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.16g, 0.40 mmol, 40%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.4 Hz, 6H), 1.70-1.96 (m, 4H), 2.17 (s, 3H), 2.64 (s, 3H), 2.66 (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. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; found: 397.2.

Example 36.

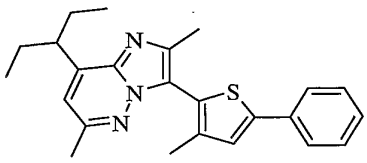
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to 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 $PdCl_2$(dppf) (0.056 g, 0.076 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (6.0 mL, 3.06 mmol) furnish the title compound (0.29 g, 0.72 mmol, 47%). ^{1}H 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), 3.31-3.40 (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. for $C_{24}H_{28}N_4$ $(M+H)^+$: 405.7; found: 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.

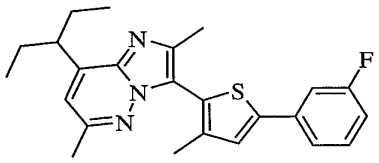


Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.05 g, 0.069 mmol) and 0.5 M solution of phenylzinc iodide in THF (5.5 mL, 2.76 mmol) furnish the title compound (0.25 g, 0.64 mmol, 50%). ^{1}H 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), 7.27-30 (m, 1H), 7.35-7.41 (m, 2H), 7.61-7.66 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.3; found: 390.3.

Example 38.

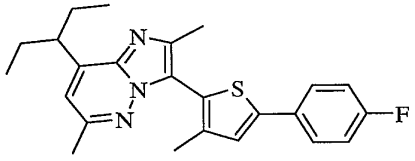
Preparation of 8-(1-ethyl-propyl)-3-[5-(3-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to 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) (0.047 g, 0.063 mmol) and 0.5 M solution of 3-flourophenylzinc iodide in THF (5.1 mL, 2.55 mmol) furnish the title compound (0.24 g, 0.59 mmol, 46%). ^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. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; found: 408.2.

Example 39.

Preparation of 8-(1-ethyl-propyl)-3-[5-(4-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

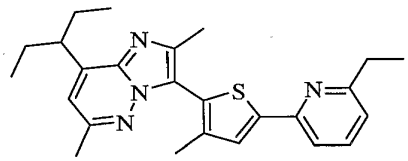


A slurry of 0.05 g/mL of Reike® Zn in THF (0.26 g, 4.01 mmol) and 1-bromo-4-fluoro-benzene (0.29 mL, 2.68 mmol) is heated at a reflux overnight. The solution is filtered under nitrogen. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.35 g, 0.89 mmol) and $PdCl_2$(dppf) (0.033 g, 0.045 mmol) are added, and the solution is heated at a reflux overnight diluted with EtOAc (30 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column

chromatography (10%-15% EtOAc/hexane gradient) furnish the title compound (0.091 g, 0.22 mmol, 25%). ^{1}H 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), 7.08 (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. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; found: 408.3.

Example 40.

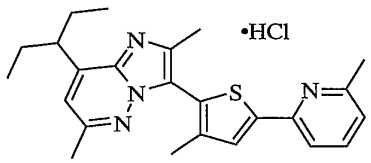
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-ethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31, 2-bromo-6-ethyl pyridine (0.26 g, 1.41 mmol), 1.56 M *n*-Bu-Li (0.94 mL, 1.47 mmol), 0.5 M $ZnCl_2$ in THF (3.0 mL, 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 $PdCl_2$(dppf) (0.047 g, 0.064 mmol) produce the title compound (0.15 g, 0.36 mmol, 28%). ^{1}H 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), 7.01 (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. for $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.3; found: 419.3.

Example 41.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine hydrochloride.

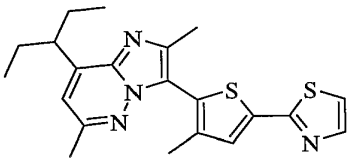


Using a procedure similar to Example 33, 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.55 g, 1.36

mmol), MeOH (6 mL) and AcCl (0.098 mL, 1.36 mmol) furnish the title compound (0.11 g, 0.25 mmol, 42%). ^{1}H NMR ($CDCl_3$), 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. for $C_{24}H_{29}ClN_4S$ $(M+H)^+$: 441.3; found: 405.2.

Example 42.

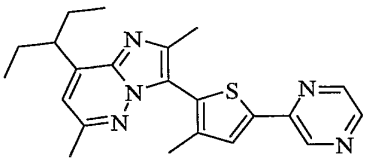
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-thiazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to 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), 0.5 M 2-thiazolylzinc bromide in THF (4.7 mL, 2.35 mmol) and $PdCl_2$(dppf) (0.043 g, 0.059 mmol) furnish the title compound (0.32 g, 0.81 mmol, 70%). ^{1}H NMR ($CDCl_3$), 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. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; found: 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.

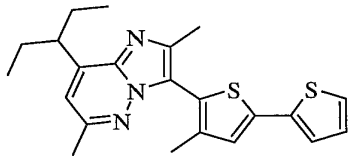


Using a procedure similar to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) (example Rupp-2), 2-chloropyrazine (0.11 mL, 1.22 mmol), 1.42 M *n*-Bu-Li (1.52 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), and $PdCl_2$(dppf) (0.037 g, 0.051

mmol) furnish the title compound (0.19 g, 0.49 mmol, 48%). ^{1}H NMR ($CDCl_3$), 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), 7.63 (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. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 44.

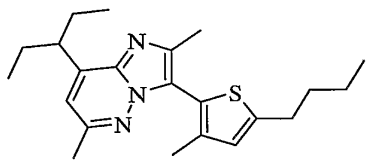
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-[2,2']bithiophenyl-5-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 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), 0.5 M 2-thiophenlyzinc bromide in THF (3.0 mL, 1.53 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) furnish the title compound (0.25g, 0.63 mmol, 83%). ^{1}H NMR ($CDCl_3$), 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, 3.6 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. for $C_{22}H_{25}N_3S_2$ $(M+H)^+$: 396.7; found: 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.

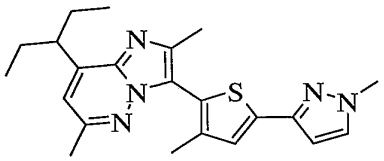


Using a procedure similar to Example 25 from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.1.02 mmol), 1.34 M *n*-Bu-Li (1.60 mL, 2.14 mmol), 0.5 M $ZnCl_2$ (4.3 mL, 2.14 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnishes the title compound (0.25g, 0.69 mmol, 68%). ^{1}H NMR

($CDCl_3$), 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): calcd. for $C_{22}H_{31}N_3S$ $(M+H)^+$: 370.3; found: 370.2.

Example 46.

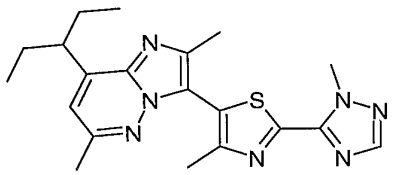
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-pyrazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



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 $ZnCl_2$ 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 $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.041g, 0.10 mmol, 10%). ^{1}H NMR ($CDCl_3$) 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): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 47.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.

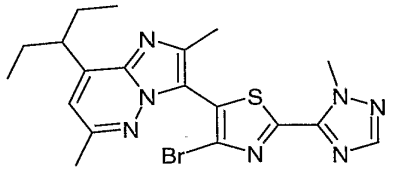


82 mg of 1-Methyl-1,2,4-triazole (0.99 mmol) is dissolved in 2 ml of dry THF and cooled to –78°C and 0.4 ml of n-butyllithium 2.5 M in hexane (0.99 mmol) is added. The reaction mixture is stirred at –78C to room temperature for 10min and cooled to –78°C

again. 1.98 ml of 0.5 M zinc chloride 0.5 M solution in THF (0.99 mmol) is added and stirred at –78C to room temperature for 15 min. 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 and the vial is capped with a Teflon cap and heated at 80°C for 2 days. The reaction is cooled to room temperature and quenched with sat. 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 : 2 M NH3 in MeOH=10:2:1) to give 57 mg of the title product. Yield 22%. mass spectrum (m/e):396(M+1). ^{1}H-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=7.3Hz, 6H).

Example 48.

Preparation of 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

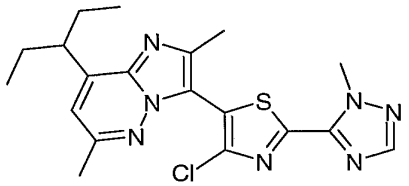


82 mg of 1-methyl-1,2,4-triazole (0.99 mmol) is dissolved in 2 ml of dry THF and cooled to –78°C and 0.4 ml of n-butyllithium 2.5 M in hexane (0.99 mmol) is added. The reaction mixture is stirred at –78°C to room temperature for 10min and cooled to –78°C again. 1.98 ml of 0.5 M zinc chloride 0.5 M solution in THF (0.99 mmol) is added and stirred at –78°C to room temperature for 15min. 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 and the vial is capped with a Teflon cap and heated at 80°C for 2days. The reaction is cooled to room temperature and quenched with sat. 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 88mg of the title product. Yield 54%.

mass spectrum (m/e):461(M+1). ^{1}H-NMR (CDCl3): 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=7.5Hz, 6H).

Example 49.

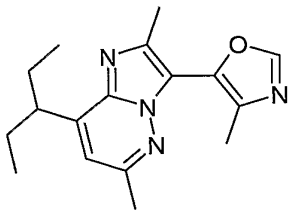
Preparation of 3-[4-chloro-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



175 mg of 3-[4-Bromo-2-(2-methyl-2*H*-[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 of copper chloride (0.57 mmol) are placed into 4 ml vial with 3.0 ml of dry DMF and the vial is capped with a Teflon cap. The vial is heated at 130°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1 and hexane:AcOEt=8:1) to give 91 mg of crude product. The pure product is recrystalized from Et2O/Hexane. 73 mg (46%). mass spectrum (m/e):416(M+1). ^{1}H-NMR (CDCl3): 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=7.5Hz, 6H).

Example 50.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-oxazol-5-yl)-imidazo[*1,2-b*]pyridazine.

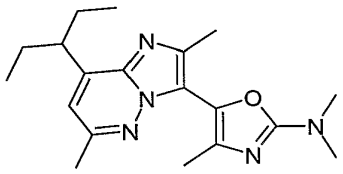


686 mg of 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 mmol), 830 mg of 4-methyl-oxazole. (10 mmol), 105 mg of triphenylphosphine (0.4 mmol) and 1.30 g of cesium carbonate (4.0 mmol) are placed into tube with 10 ml of dry

DMF. N2 gas is bubbled in for 20min and 92 mg of Pd2dba3 (0.1 mmol) is added. The tube is sealed and heated at 130°C overnight. After being cooled to room temperature, water and CHCl2 are added to the mixture. The CHCl2 layer is separated, washed with sat. 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). ^{1}H-NMR (CDCl3): 8.06 (s, 1H), 6.75 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.50 (s, 3H), 2.29 (s, 3H), 1.86 (m, 4H), 0.90 (t, J=7.4Hz, 6H).

Example 51.

Preparation of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-oxazol-2-yl}-dimethylamine.



A. 3-(2-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 of CH2Cl2 and 178 mg of NBS (1.0 mmol) is added. The reaction mixture is stirred at room temperature overnight. The reaction mixture is washed with sat. Na2S2O3, sat. 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). ^{1}H-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=7.4Hz, 6H).

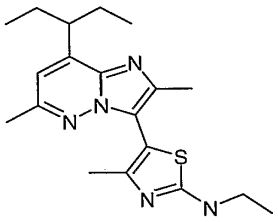
B. N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-oxazol-2-yl}-dimethylamine.

32 mg of 3-(2-Bromo-4-methyl-oxazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.08 mmol) and 78 mg of cesium carbonate (0.24 mmol) are placed into vial with 3 ml of dimethylamine 2.0 M in THF. The vial is capped with a

Teflon cap and heated at 110°C for 3days. 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). ^{1}H-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=7.5Hz, 6H).

Example 52.

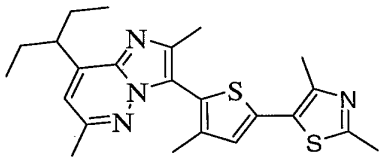
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[(4-methyl-2-ethylamino)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.



The title compound is prepared essentially as described in Example 51B. employing 2.0 ml of ethylamine 2.0 M in THF and 182 g of cesium carbonate (0.56 mmol), 78%. 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=7.2Hz), 0.90(t, 6H, J=7.2Hz).

Example 53.

Preparation of 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.

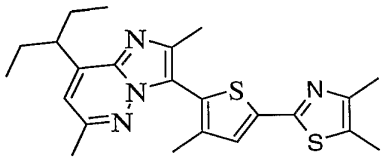


To a –78 °C mixture of 2,4-dimethylthiazole (0.23 g, 2.04 mmol) and THF (3 mL) is added 1.6 M *t*-Bu-Li in hexane (1.30 mL, 2.09 mmol). The mixture is stirred at –78°C for 15 minutes. 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-

2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65 °C overnight, diluted with EtOAc (20 mL), washed with 10% citric acid (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by silica gel chromatography (0%-15% EtOAc/hexane gradient) furnish the title compound (0.21 g, 0.49 mmol, 49%). ^{1}H NMR ($CDCl_3$), δ 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. for $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; found: 425.2.

Example 54.

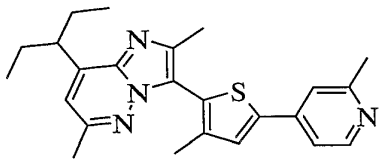
Preparation of 3-[5-(4,5-dimethyl-thiazol-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, from 4,5-dimethylthiazole (0.22 mL, 2.04 mmol), 1.56 M *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 $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.27 g, 0.64 mmol, 63%). ^{1}H NMR ($CDCl_3$), δ 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. for $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; found: 425.2.

Example 55.

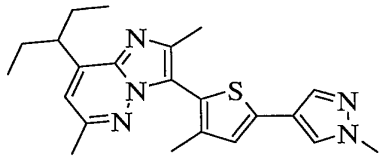
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-pyridin-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31, from 4-bromo-2-methyl pyridine (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), 0.5 M $ZnCl_2$ in THF (2.2 mL, 1.12 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 $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.058 g, 0.14 mmol, 14%). ^{1}H NMR ($CDCl_3$), δ 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. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.2.

Example 56.

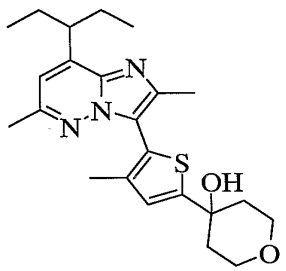
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-pyrazol-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 31, from 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 $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 4-bromo-1-methyl-*1H*-pyrazole (0.25 g, 1.53 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnishes the title compound (0.092g, 0.23 mmol, 23%). ^{1}H NMR ($CDCl_3$) δ 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), 6.66 (s, 1H), 6.98 (s, 1H), 7.54 (s, 1H), 7.68 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 57.

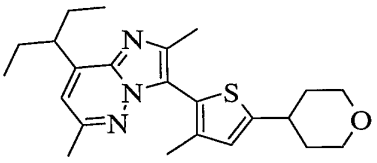
Preparation of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-tetrahydro-pyran-4-ol.



To a -78°C solution of 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) is added 1.56 M *n*-Bu-Li (1.03 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 hours, warmed to ambient temperature, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-100% EtOAc/hexane gradient) furnish the title compound (0.38 g, 0.92 mmol, 60%). ^1H NMR ($CDCl_3$), δ 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), 3.83-3.98 (m, 5H), 6.66 (s, 1H), 6.93 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{31}N_3O_2S$ $(M+H)^+$: 414.3; found: 414.2.

Example 58.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(tetrahydro-pyran-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Method A.

To a solution of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-tetrahydro-pyran-4-ol (0.25 g, 0.604 mmol) and CH_2Cl_2

(10 mL) is added TFA (0.79 mL, 10.28 mmol) and Et_3SiH (0.25 mL, 1.57 mmol). The solution is concentrated, dissolved in EtOAc (30 mL), washed with sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-15% EtOAc/hexane gradient), is dissolved in EtOH (25 mL), 10 % Pd/C (0.07 g, 0.066 mmol) is added and the solution stirred under an atmosphere of H_2. After 2 hours the solution is filtered thru celite® and concentrated. The residue is purified by ISCO column chromatography (30% EtOAc in hexane) furnish the title compound (0.033 g, 0.083 mmol, 14%). ^1H 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), 4.08 (dd, J = 11.8, 2.2 Hz, 2H), 6.65 (s, 1H), 6.75 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{31}N_3OS$ $(M+H)^+$: 398.7; found: 398.2.

Method B.

A. 4-(5-Bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol.

To a -78°C solution of 2-bromo-3-methyl-thiophene (2.0 g, 17.75 mmol) and THF (30 mL) is added 2.0 M LDA (9.32 mL, 18.63 mmol). After 30 minutes at –78°C tetrahydro-pyran-4-one (2.3 mL, 23.07 mmol) is added and the solution is warmed to ambient temperature. The solution is washed with sat. NH_4Cl (30 mL). The aqueous phases is extracted with EtOAc. The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (30%-100% EtOAc/hexane gradient) furnish the title compound (2.3 g, 8.30 mmol, 47%). ^1H 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. for $C_{10}H_{13}BrO_2S$ $(M+H)^+$: 277.0; found: 260.9.

B. 4-(5-Bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran.

To a solution of 4-(5-bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol (2.3 g, 8.30 mmol) and 1,2-dichloroethane (50 mL) is added ZnI_2 (3.97 g, 12.45 mmol) and sodium cyanoborohydride (3.91, 62.23 mmol). The solution is stirred for 1 hour, filtered

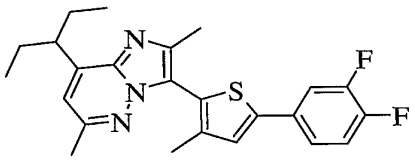
thru celite and concentrated. The residue is purified by ISCO column chromatography (5%-10% EtOAc/hexane gradient) furnish the title compound (1.53 g, 5.86 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 1.69-1.82 (m, 2H), 1.84-1.92 (m, 2H), 2.14 (s, 3H), 2.84-2.98 (m, 1H), 3.49 (dt, J = 11.8, 2.2 Hz, 2H), 4.00-4.07 (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 Example 25, 4-(5-bromo-4-methyl-thiophen-2-yl)-tetrahydropyran (0.83 g, 3.19 mmol), 1.56 M *n*-Bu-Li (2.04 mL, 3.19 mmol), $ZnCl_2$ (6.4 mL, 3.19 mmol), 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.56 mmol) and $Pd(PPh_3)_4$ (0.092 g, 0.008 mmol) furnish the title compound (0.072 g, 0.18 mmol, 11%). Spectrum identical to that from Method A.

Example 59.

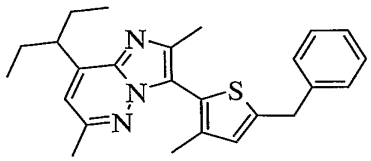
Preparation of 3-[5-(3,4-difluoro-phenyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to 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) (0.047 g, 0.064 mmol) and 0.5 M solution of 3,4-difluorophenylzinc bromide in THF (5.1 mL, 2.55 mmol) are reacted. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 30-80% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.18 g, 0.42 mmol, 33%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.16 (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. for $C_{24}H_{25}F_2N_3S$ $(M+H)^+$: 426.3; found: 426.2.

Example 60.

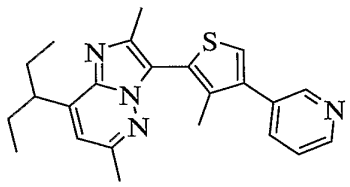
Preparation of 3-(5-benzyl-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to 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) (0.028 g, 0.038 mmol) and 0.5 M solution of benzylzinc bromide in THF (4.6 mL, 2.29 mmol) are reacted. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 40-65% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.062 g, 0.15 mmol, 20%). ^{1}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. for $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; found: 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.

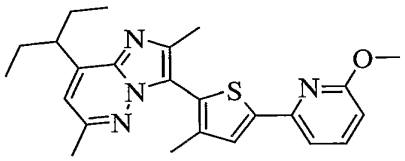


A solution of 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.64 mmol), pyridine-3-boronic acid (0.086 g, 0.70 mmol), 2 M Na_2CO_3 (0.48 mL, 0.96 mmol) and, *n*-PrOH (3 mL), is degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (2.7 mg, 0.0013 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) furnish the title compound (0.051 g, 0.13 mmol, 20%). ^{1}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. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2; found: 391.4.

Example 62.

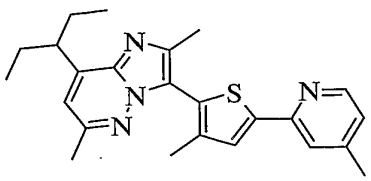
Preparation of 8-(1-ethyl-propyl)-3-[5-(6-methoxy-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 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) (0.028 g, 0.038 mmol) and 0.5 M solution of 6-methoxy-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.12 g, 0.29 mmol, 38%). ^{1}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. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; found: 421.3.

Example 63.

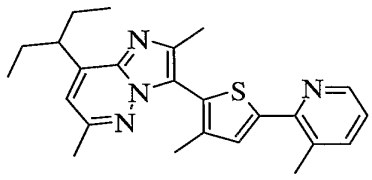
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(4-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 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) (0.028 g, 0.038 mmol) and 0.5 M solution of 4-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.21 g, 0.52 mmol, 68%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.40 (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. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 64.

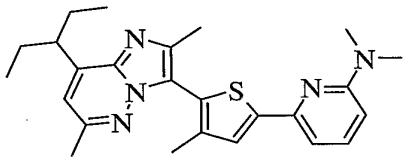
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(3-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 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) (0.028 g, 0.038 mmol) and 0.5 M solution of 3-methyl-2-pyridylzinc bromide in THF (5.0 mL, 2.50 mmol) furnish the title compound (0.22 g, 0.54 mmol, 71%). ^{1}H 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), 2.51 (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): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 65.

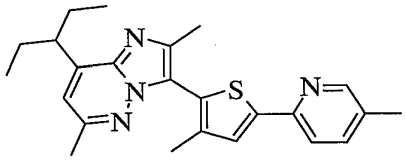
Preparation of (6-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-dimethyl-amine.



Using a procedure similar to Example 39, from Rieke® Zn in THF (0.20 g, 3.06 mmol), (6-bromo-pyridin-2-yl)-dimethyl-amine (Newkomw et. el. *J. Org. Chem.*, 1988, 3, 786) (0.41 mL, 2.04 mmol), 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 $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.16 g, 0.37 mmol, 36%). ^{1}H NMR ($CDCl_3$), 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. for $C_{25}H_{31}N_5S$ $(M+H)^+$: 434.3; found: 434.3.

Example 66.

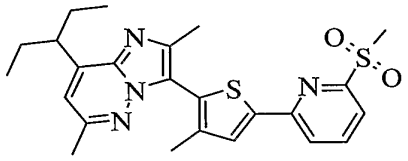
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 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) (0.028 g, 0.038 mmol) and 0.5 M solution of 4-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.23 g, 0.57 mmol, 74%). ^{1}H NMR ($CDCl_3$), 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. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 67.

Preparation of 8-(1-ethyl-propyl)-3-[5-(6-methanesulfonyl-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 2-Bromo-6-methanesulfonyl-pyridine.

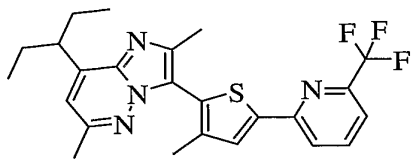
To a solution of 2-bromo-6-methylsulfanyl-pyridine (Testaferri et. el *Tetrahedron*, 1985, 41, 1373) (2.15 g, 10.53 mmol) and CH_2Cl_2 (30 mL) is added 56-87% mCPBA (12 g, 42.15 mmol). The solution is cooled with ice to ambient temperature and the solution is stirred for 2 hour, washed with sat. $Na_2S_2O_3$ (15 mL), sat. $NaHCO_3$ (2 X 15 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by recrystalization from EtOAc /hexane furnish the title compound (1.71 g, 7.24 mmol, 69%). ^1H NMR ($CDCl_3$), 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. for $C_6H_6BrNO_2S$ $(M+H)^+$: 235.9; found: 235.9.

B. 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 Example 25, 2-bromo-6-methanesulfonyl-pyridine (0.29 mL, 1.22 mmol), 1.3 M *n*-Bu-Li (0.82 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, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.13 g, 0.28 mmol, 27%). ^1H NMR ($CDCl_3$), 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. for $C_{24}H_{28}N_4O_2S_2$ $(M+H)^+$: 469.3; found: 469.2.

Example 68.

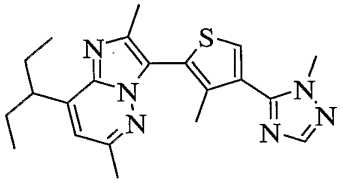
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



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), $ZnCl_2$ (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, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.20 g, 0.44 mmol, 43%). ^{1}H NMR ($CDCl_3$), 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), 6.69 (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. for $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; found: 459.2.

Example 69.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-4-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

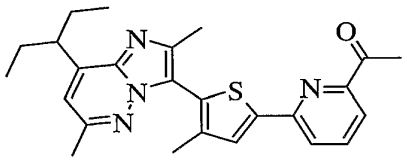


To a slurry of 0.05 g/ mL of Reike® Zn in THF (3.0 mL, 2.29 mmol) is added a solution of 5-bromo-1-methyl-*1H*-[1,2,4]triazole and THF (2 mL). The solution was heated at 65 °C for 1 hour, cooled to ambient temperature and the excess Zn allowed to settle for 1 hour. The solution was transferred to a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example Rupp-152) (0.32 g, 0.70 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat.

NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (50%-100% Et_2O) to furnish the title compound (0.058 g, 0.15 mmol, 19%). ^1H NMR ($CDCl_3$) 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), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.2; found: 395.4.

Example 70.

Preparation of 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.



A. 3-[5-(6-Bromo-pyridin-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*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), $ZnCl_2$ (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) and $PdCl_2$(dppf) (0.070 g, 0.096 mmol) furnish the title compound (0.26 g, 0.55 mmol, 29%). ^1H NMR ($CDCl_3$), 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).

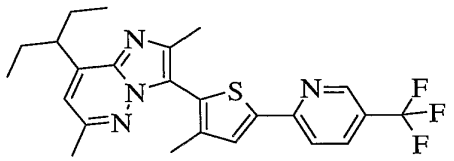
B. 1-(6-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-ethanone.

To a –78°C solution of 3-[5-(6-bromo-pyridin-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine) (0.26 g, 0.55 mmol), and THF (5 mL), is added 1.34 M *n*-Bu-Li (0.43 mL, 0.58 mmol). After 30 minutes *N*-methoxy-*N*-methyl-acetamide (0.065 mL, 0.61 mmol) is added and the solution warmed to ambient

temperature. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15-20% EtOAc/hexane gradient) furnish the title compound (0.030 g, 0.069 mmol, 13%). ^1H 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), 6.69 (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. for $C_{25}H_{28}N_4OS$ $(M+H)^+$: 433.3; found: 433.2.

Example 71.

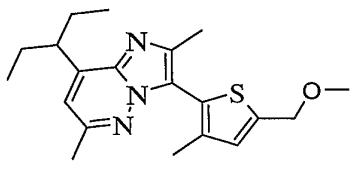
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 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, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.17 g, 0.37 mmol, 36%). ^1H 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), 6.70 (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. for $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; found: 459.2.

Example 72.

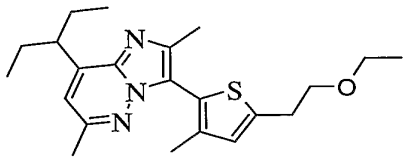
Preparation of 8-(1-ethyl-propyl)-3-(5-methoxymethyl-3-methyl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78°C solution of 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) 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 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%-20% EtOAc/hexane gradient) furnish the title compound (0.12 g, 0.34 mmol, 44%). ^{1}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), 6.65 (s, 1H), 6.93 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{27}N_3OS$ $(M+H)^+$: 358.3; found: 358.3.

Example 73.

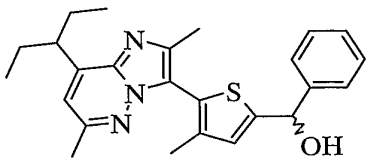
Preparation of 3-[5-(2-ethoxy-ethyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 72, from of 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) furnish the title compound (0.11 g, 0.29 mmol, 38%). ^{1}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), 2.06 (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): calcd. for $C_{22}H_{31}N_3OS$ $(M+H)^+$: 386.3 found: 386.3.

Example 74.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanol.



A. (5-Bromo-4-methyl-thiophen-2-yl)-phenyl-methanol.

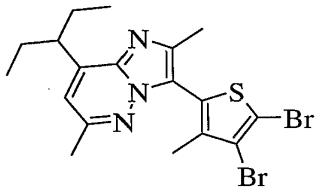
To a –78°C solution of 2-bromo-3-methyl-thiophene (4.7 g, 26.54 mmol) and Et_2O (100 mL) is added 2.0 M LDA (14.6 mL, 29.2 mmol). After 1 hour benzaldehyde (3.0 mL, 29.2 mmol) is added and the solution warmed to ambient temperature and stirred for 2 hour. The solution is washed with sat. NH_4Cl (75 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (3.29 g, 11.62 mmol, 44%). ^{1}H NMR ($CDCl_3$), δ 2.11 (s, 3H), 3.38-3.46 (m, 1H), 5.90 (s, 1H), 6.54 (s, 1H), 7.30-7.45 (m, 5H). LC/MS (m/z): calcd. for $C_{12}H_{11}BrOS$ $(M+H)^+$: 281.0, 283.0; found: 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-methanol.

Using a procedure analogous to Example 30C, from 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.1.15 mmol), (5-bromo-4-methyl-thiophen-2-yl)-phenyl-methanol (0.33 g, 1.15 mmol), 2 M Na_2CO_3 (0.86 mL, 1.72 mmol) *n*-PrOH (1 mL), $Pd(OAc)_2$ (0.0052 g, 0.023 mmol), and PPh_3 (0.018 , 0.069 mmol). The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 25-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.017 g, 0.041 mmol, 3.5%). ^{1}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. for $C_{25}H_{29}N_3OS$ $(M+H)^+$: 420.3; found: 420.3.

Example 75.

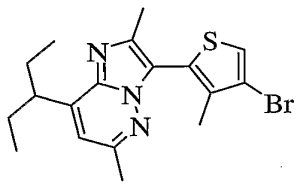
Preparation of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (4.00 g, 10.20 mmol) and AcOH (40 mL) is added Br_2 (0.57 mL, 11.21 mmol) and the solution heated at 110 °C overnight. Br_2 (0.57 mL, 11.21 mmol) is added and the solution heated at 110 °C for 2 hours. The solution is poured into 5 M 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), sat. $NaHCO_3$ (200 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (5%-15% EtOAc gradient) furnish the title compound (2.66 g, 5.64 mmol, 55%). ^1H 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. for $C_{18}H_{21}Br_2N_3S$ $(M+H)^+$: 470.0; found: 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.

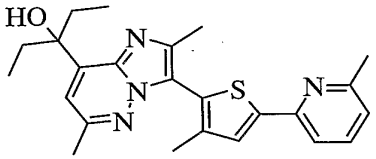


To a –78 °C solution of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 g, 0.47 mmol) and THF (3 mL) is added 1.6 M *n*-BuLi (0.31 mL, 0.49 mmol). After 20 minutes the solution is quenched with water (1 mL), warmed to ambient temperature, diluted with EtOAc (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified

by ISCO (5%-10% EtOAc gradient) furnish the title compound (0.056 g, 0.14 mmol, 31%). ^{1}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. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; found: 392.3.

Example 77.

Preparation of 3-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol.



A. 2-(5-Bromo-4-methyl-thiophen-2-yl)-6-methyl-pyridine.

To a –78°C solution of 2-bromo-3-methyl-thiophene (2.0 mL, 17.75 mmol) and THF (30 mL) is added 2.0 M LDA (9.76 mL, 19.52 mmol). After 45 minutes 0.5 M $ZnCl_2$ (39.0 mL, 19.50 mmol) is added and the solution stirred for 30 minutes. 2-Bromo-6-methyl-pyridine (2.4 mL, 21.29 mmol) and $Pd(PPh_3)_4$ (0.50 g, 0.44 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hour. The solution is washed with sat. NH_4Cl (20 mL). The aqueous layer is extracted with CH_2Cl_2 (30 mL). The combined organic layers are washed with sat. NH_4Cl (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-20% EtOAc/hexane gradient) furnish the title compound (2.34 g, 8.73 mmol, 49%). ^{1}H 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): calcd. for $C_{11}H_{10}BrNS$ $(M+H)^+$: 267.0, 269.0; found:267.7, 269.5.

B. 2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine (below) (0.50 g, 3.39 mmol), 2-(5-bromo-4-methyl-thiophen-2-yl)-6-methyl-pyridine (1.00 g, 3.73 mmol), Cs_2CO_3 (2.32 g, 7.13 mmol) and DMF (5 mL) is de-gassed for 15 minutes with N_2. $Pd_2(dba)_3$ (0.15 g, 0.16 mmol) and PPh_3 (0.17 g, 0.65 mmol) is 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), followed by recrystalization from acetonitrile / water furnish the title compound (0.45 g, 1.35 mmol, 39%). ^{1}H 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. for $C_{19}H_{18}N_4S$ $(M+H)^+$: 335.1; found: 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.

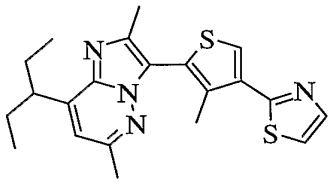
To a –78°C solution of 2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.34 g, 1.02 mmol) and THF (9 mL) is added 2.0 M LDA (0.61 mL, 1.22 mmol). After 3 minutes, *N*-methoxy-*N*-methyl-propionamide (Wolberg et. el. *Chem. Eur. J.*, 2001, 7, 4562) (1.17 g, 1.42 mmol) is added and the solution stirred for 20 minutes, warmed to ambient temperature and stirred for 30 minutes. The solution is diluted with EtOAc (50 mL) washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.10 g, 0.26 mmol, 25%). ^{1}H 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. for $C_{22}H_{22}N_4OS$ $(M+H)^+$: 391.2; found: 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}-pentan-3-ol.

To a –0°C solution of 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 Et_2O (5 mL) is added 3.0 M ethyl magnesium bromide (0.68 mL, 2.05 mmol). The solution is warmed to ambient temperature, diluted with EtOAc (30 mL) washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.016 g, 0.038 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), 6.39 (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. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; found: 421.3.

Example 78.

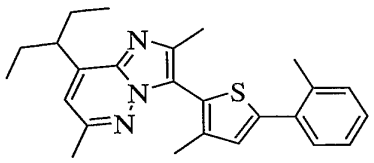
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-thiazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 g, 0.64 mmol) and $PdCl_2$(dppf) (0.023 g, 0.032 mmol) is added a 0.5 M solution of 2-thiazolylzinc bromide (3.82 mL, 1.91 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-20% EtOAc gradient) furnish the title compound (0.19 g, 0.48 mmol, 76%). ^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 (, 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. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.2; found: 397.3.

Example 79.

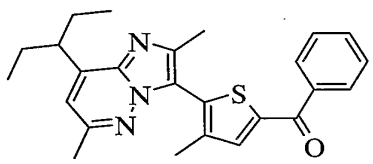
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-o-tolyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 g, 0.38 mmol) and $PdCl_2$(dppf) (0.014 g, 0.019 mmol) and 0.5M solution of 2-methylphenylzinc iodide in THF (3 mL, 1.53 mmol) furnish the title compound (0.069 g, 0.17 mmol, 46%). ^{1}H 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. for $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; found: 404.3.

Example 80.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanone.

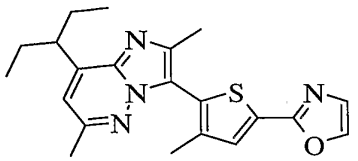


To a -78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and THF (5 mL) is added 1.30 M *n*-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes *N*-methoxy-*N*-methyl-benzamide (0.13 mL, 0.84 mmol) is added, the solution is warmed to ambient temperature, and stirred overnight. The solution is diluted with EtOAc (20 mL), washed with sat. 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%-20% EtOAc/hexane gradient) furnish the title compound (0.066 g, 0.16 mmol, 21%). ^{1}H 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. for $C_{25}H_{27}N_3OS$ $(M+H)^+$: 418.2; found: 418.2.

Example 81.

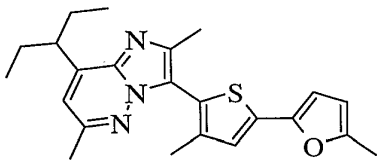
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-oxazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of oxazole (0.14 g, 2.04 mmol) and THF (3 mL) 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. 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed 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 $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65 °C overnight, diluted with EtOAc (30 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 20-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) to furnish the title compound (0.020 g, 0.053 mmol, 5%). ^{1}H 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): calcd. for $C_{21}H_{24}N_4OS$ $(M+H)^+$: 381.3; found: 381.1.

Example 82.

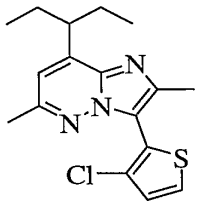
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-methyl-furan-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



To a 0°C mixture of 2-methylfuran (0.18 mL, 2.04 mmol) and Et_2O (2 mL) is added 1.6 M *t*-Bu-Li in hexane (1.30 mL, 2.14 mmol). The mixture is heated at a reflux for 30 minutes, cooled to 0°C, and 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed 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 $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65°C overnight, diluted with EtOAc (30 mL), washed with 10% citric acid (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc/hexane gradient) furnish the title compound (0.20 g, 0.51 mmol, 50%). ^{1}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), 6.62 (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. for $C_{23}H_{27}N_3OS$ $(M+H)^+$: 394.3; found: 394.2.

Example 83.

Preparation of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

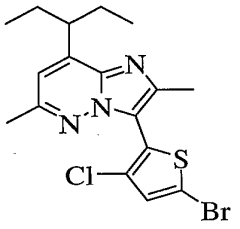


To a flask of 2-bromo-3-chloro-thiophene (Lemaire et. el., *Synth. Commun.*, 1994, 24, 95) (2.53 g, 12.82 mmol) is added 0.05 g/mL Reike® zinc in THF (25 mL, 19.24 mmol). The solution is heated at a reflux for 2 hours. The excess zinc is allowed to settle and the solution transferred to a flask containing 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example KW1-A03735-193) (2.01 g, 6.41 mmol) and $PdCl_2$(dppf) (0.23 g, 0.32 mmol). The solution is heated at a reflux overnight, quenched with sat. NH_4Cl (25 mL) and extracted with EtOAc (2 X 25 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (2%-15% EtOAc/hexane gradient) furnish the title compound (1.32 g, 6.68 mmol, 62%). ^{1}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. for $C_{17}H_{20}ClN_3S$ $(M+H)^+$: 334.1; found: 334.1.

Example 84.

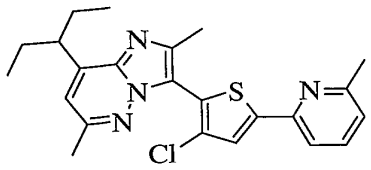
Preparation of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine. (1.15 g, 3.44 mmol) and CH_2Cl_2 (12 mL) is added NBS (0.64 g, 3.62 mmol). The solution is stirred at ambient temperature overnight, washed with water (2 x 75 mL), brine (75 mL), dried over Na_2SO_4, filtered and concentrated to furnish the title compound (1.36 g, 3.29 mmol, 96%). ^{1}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), 3.26-3.36 (m, 1H), 6.70 (s, 1H), 7.07 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.1; found: 412.0.

Example 85.

Preparation of 3-[3-chloro-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

To a flask of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.73 mmol) and $PdCl_2$(dppf) (0.027 g, 0.036 mmol) is added 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (2.9 mL, 1.45

mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (50 mL), washed with sat. 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%-40% EtOAc/hexane gradient) furnish the title compound (0.072 g, 0.17 mmol, 23%). ^1H 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. for $C_{23}H_{25}ClN_4S$ $(M+H)^+$: 425.2; found: 425.2.

Method B.

A. 2-(4-Chloro-thiophen-2-yl)-6-methyl-pyridine.

To a solution of 2-bromo-4-chloro-thiophene (Gronowitz, Rosén *Chemica Scripta*, 1971, 1, 33) (1.50 g, 7.60 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (23.00 mL, 11.39 mmol) is added $Pd(PPh_3)_4$ (0.18 g, 0.15 mmol). The solution is heated at 40°C overnight, diluted with Et_2O (50 mL), washed with sat. NH_4Cl (40 mL), dried over $MgSO_4$, filtered on concentrated. The residue is purified by ISCO column chromatography (5%-20% EtOAc/hexane gradient) furnish the title compound (0.45 g, 2.15 mmol, 28%). ^1H 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.

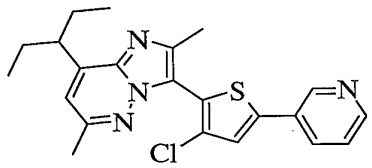
To a 0°C solution of 2-(4-chloro-thiophen-2-yl)-6-methyl-pyridine (example Rupp-96) (0.45 g, 1.45 mmol) and CH_2Cl_2 (10 mL) is added Br_2 (0.15 mL, 2.91 mmol). The solution is warmed to ambient temperature and stirred for 1 hour. The solution is washed with sat. $NaHCO_3$ (10 mL), sat. $Na_2S_2O_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.59 g, 2.04, 95%). ^1H 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): calcd. for $C_{10}H_7BrClNS$ $(M+H)^+$: 288.0; found: 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.

A solution of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.39 g, 1.78 mmol), 2-(5-bromo-4-chloro-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), is de-gassed with N_2 for 15 minutes. PPh_3 (0.089 g, 0.34 mmol) and $Pd_2(dba)_3$ (0.079 g, 0.86 mmol) is added and the solution heated at 110°C for 48 hours. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) and is chromatographed (19 x 300 C18 Symmetry column, 20-45% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.078 g, 0.18 mmol, 10%). Spectrum identical to 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.

A solution of 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), pyridine-3-boronic acid (0.082 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol) and, *n*-PrOH (1 mL), is degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (0.0027 g, 0.0012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added and the solution is heated at 88°C overnight. The solution is diluted with EtOAc (15 mL), washed with water (10 mL), sat. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO column chromatography (15-40% EtOAc/hexane gradient) furnish the title compound (0.095 g, 0.23 mmol, 38%). ^1H 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), 7.85-7.90 (m, 1H), 8.57 (d, J = 4.0 Hz, 1H), 8.89 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.2; found: 411.2.

Method B.

A. 3-(4-Chloro-thiophen-2-yl)-pyridine.

A solution of 2-bromo-4-chloro-thiophene (Gronowitz, Rosén *Chemica Scripta*, 1971, 1, 33) (1.45 g, 7.34 mmol), pyridine-3-boronic acid (0.95 g, 7.71 mmol), 2 M Na_2CO_3 (5.50 mL, 11.01 mmol) and, *n*-PrOH (3 mL), is degassed with N_2 for 10 minutes. $Pd(OAc)_2$ (0.033 g, 0.15 mmol) and PPh_3 (0.12 g, 0.44 mmol) are added and the solution is heated at 85°C for 48 hours, diluted with CH_2Cl_2 (50 mL), washed with 10 % Na_2CO_3 (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.74 g, 3.78 mmol, 51%). ^{1}H 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.

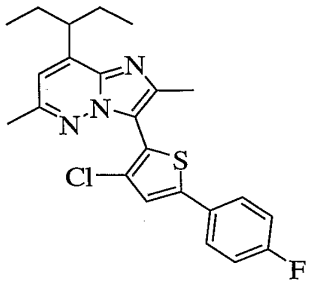
Using a procedure similar to Example 85 Method B. step B, 3-(4-chloro-thiophen-2-yl)-pyridine (0.74 g, 3.78 mmol), and Br_2 (0.39 mL, 7.56 mmol) furnish the title compound (0.99 g, 3.61 mmol, 95%). ^{1}H NMR ($CDCl_3$), δ 7.13 (s, 1H), 7.34 (dd, J = 8.1, 4.4 Hz, 1H), 7.74-7.78 (m, 1H), 8.58 (d, J = 4.4 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.

Using a procedure similar to Example 85 Method B Step C, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 2.30 mmol), 3-(5-bromo-4-chloro-thiophen-2-yl)-pyridine) (0.76 g, 2.76 mmol), Cs_2CO_3 (1.57 g, 4.83 mmol), PPh_3 (0.11 g, 0.44 mmol) and $Pd_2(dba)_3$ (0.10 g, 0.11 mmol). The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.35 g, 0.85 mmol, 37%). Spectrum identical to Method A.

Example 87.

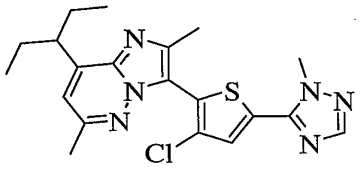
Preparation of 3-[3-chloro-5-(4-fluoro-phenyl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 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), 4-flourophenylboronic acid (0.093 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol), *n*-PrOH (2 mL), $Pd(OAc)_2$ (0.0068 g, 0.030 mmol) and PPh_3 (0.016 g, 0.061 mmol) furnish the title compound (0.041 g, 0.096 mmol, 16%). ^{1}H 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), 6.70 (s, 1H), 7.07-7.13 (m, 2H), 7.22 (s, 1H), 7.54-7.60 (m, 2H). LC/MS (m/z): calcd. for $C_{23}H_{23}ClFN_3S$ $(M+H)^+$: 428.2; found: 428.1.

Example 88.

Preparation of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

To a –78 °C solution of 1-methyl-1,2,4-triazole (0.18 mL, 2.33 mmol) and THF (3 mL) is added a 1.56 M solution of *n*-Bu-Li in hexanes (1.49 mL, 2.33 mmol). The solution is stirred at –78°C for 30 minutes, 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution 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,

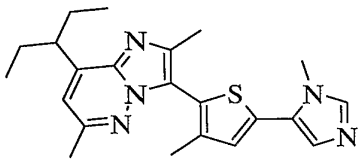
0.78 mmol) and $PdCl_2$(dppf) (0.028 g, 0.039 mmol) is added and the solution heated at 60 °C for 2 days, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (30 mL), water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-10% EtOAc/hexane gradient) furnish 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. for $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; found: 415.1.

Method B.

A 5-L reaction flask equipped with a cooling bath, air stirrer, gas dispersion tube and thermometer probe is charged with 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-1H-[1,2,4]triazole (162.0 g, 0.745 moles), 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (250.1 g, 0.898 moles), NMP (800 mL), KOAc (366.0 g), TBABr (50.5 g), and additional NMP (700 mL) to form a mixture. While stirring, N_2 is bubbled through the mixture for 1 hour. A mixture of $Pd(OAc)_2$ (8.37 g) and TDBPP (24.56 g) are added in one portion, then heated to 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, then added de-ionized H_2O (3.5 L) is added dropwise to precipitate out a sticky solid that gradually solidifies with stirring overnight. The solids are filtered, washed with de-ionized H_2O (2 x 2L), and fried on the filter plate for 30-60 minutes. The crude solids (595 g) are warmed in EtOAc (6.0 L) to 30 °C, then filtered through GFF paper to remove insolubles. The filtrate is dried over Na_2SO_4, treated with Darco (30.0 g), heated to 35 °C, filtered, and concentrated to give brown solids (432 g). The crude solids are eluted through 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 under vacuum to approximately 6.0 L, then treated with Darco overnight with stirring. After filtering off the Darco through GFF paper, the filtrate is concentrated to solids (336 g). The solids are crystallized from EtOAc: heptane (1:2) to afford 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., oven temp. 25°C, isocratic = 30% water (0.1% TFA) & 70% AcCN.

Example 89.

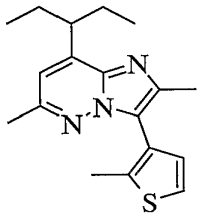
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(3-methyl-*3H*-imidazol-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using the 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), 1.34M *n*-Bu-Li (0.80 mL, 1.07 mmol), 0.5M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 5-iodo-1-methyl-*1H*-imidazole (0.24 g, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.061g, 0.15 mmol, 15%). ^{1}H 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. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 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.

A mixture of 3-bromo-2-methyl-thiophene (Saika et. el. *Chem. Soc. Chem. Communication*, 18, 1994, 2133; Steinkopf et. el.; *Justus Liebigs Ann. Chem.*, 513, 1934, 281; 3.1 g, 17.51 mmol), DMSO (50 mL), 4,4,5,5,4',4',5',5'-Octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (4.90g, 19.26 mmol), and KOAc (5.20 g, 52.58 mmol) is de-gassed with N_2 for 15 minutes. $PdCl_2$(dppf) (0.70 g, 0.88 mmol) is added and the solution stirred at ambient temperature overnight, then warmed to 85°C for 3 hours. The solution is diluted with water (200 mL), extracted with EtOAc (2 x 100 mL). The

combined organic layers 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%-20% EtOAc/hexane gradient) furnish the title compound (1.52 g, 6.78 mmol, 39%). ^{1}H 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.

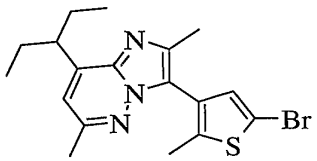
To a solution of 4,4,5,5-tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane (1.52 g, 6.78 mmol), acetone (15 mL) and water (15 mL) is added $NaIO_4$ (2.90 g, 13.56 mmol). The solution is stirred at ambient temperature for 24 hours, then heated to a reflux for 24 hours. The solution is concentrated dissolved in EtOAc (1450 mL), washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.75g, 5.49 mmol, 78%). ^{1}H 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.

(1.65 g, 4.80 mmol), 2-methyl-thiophene-3-boronic acid (0.75 g, 5.28 mmol), 2 M Na_2CO_3 (3.60 mL, 7.20 mmol) and *n*-PrOH (20 mL) is degassed with N_2 for 10 minutes. $Pd(OAc)_2$ (0.022 g, 0.096 mmol) PPh_3 (0.076 g, 0.29 mmol) is added and the solution heated at 60°C for 24 hours, then heated at 90°C for 24 hours. The solution is concentrated, diluted in EtOAc (50 mL) washed with 10% Na_2CO_3 (40 mL), water (40 mL), brine (40 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-15% EtOAc/hexane gradient) furnish the title compound (0.78 g, 2.49 mmol, 52%). ^{1}H 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), 7.20 (d, J = 5.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.2; found: 314.2.

Example 91.

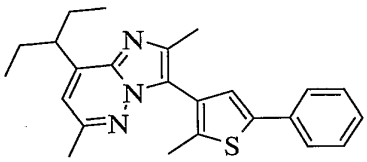
Preparation of 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 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 (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 furnish the title compound (0.95 g, 2.42 mmol, >99%). ^{1}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. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; found: 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.

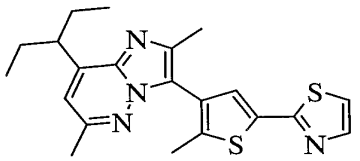


Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol) and $PdCl_2$(dppf) (0.019 g, 0.025 mmol) and 0.5 M solution of phenylzinc iodide in THF (2.0 mL, 1.02 mmol). The residue is purified by column chromatography (0-10% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.081 g, 0.21 mmol, 41%). ^{1}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): calcd. for $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.2; found: 390.2.

Example 93.

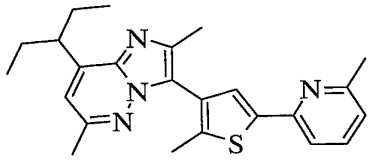
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 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), 0.5 M 2-thiazolylzinc bromide in THF (8.1 mL, 4.05 mmol) and $PdCl_2$(dppf) (0.019 g, 0.025 mmol) furnish the title compound (0.20 g, 0.50 mmol, >99%). ^{1}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. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.1; found: 397.2.

Example 94.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[2-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-3-yl]-imidazo[*1,2-b*]pyridazine.

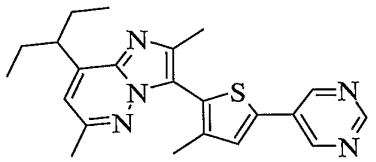


Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.24 g, 0.61 mmol) and $PdCl_2$(dppf) (0.022 g, 0.031 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (3.7 mL, 1.84 mmol) furnish the title compound (0.086 g, 0.21 mmol, 34%). ^{1}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. for $C_{24}H_{28}N_4$ $(M+H)^+$: 405.2; found: 405.2.

Example 95.

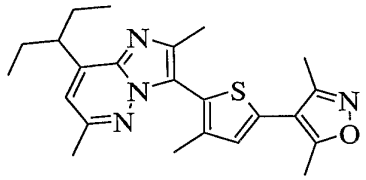
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrimidin-5-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 74B, from of 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-pyrimidine boronic acid (0.076 g, 0.61 mmol), 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), $Pd(OAc)_2$ (0.0023 g, 0.011 mmol), PPh_3 (0.0080 g, 0.0031 mmol), and *n*-PrOH (2 mL) is furnished the title compound (0.084 g, 0.21 mmol, 42%). ^1H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.17 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.69 (s, 1H), 7.74 (s, 1H), 8.95 (s, 2H), 9.10 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 96.

Preparation of 3-[5-(3,5-Dimethyl-isoxazol-4-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

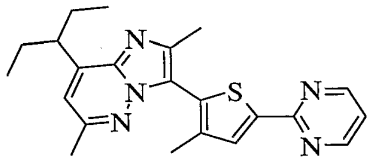


To a flask of 4-iodo-3,5-dimethyl-isoxazole (0.34 g, 1.53 mmol) is added a solution of Rieke® zinc 5g/100 mL in THF (3 mL, 2.29 mmol). The slurry is heated at a reflux for 4 hours, the zinc is allowed to settle and the solution transferred to a flask of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and $PdCl_2$(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. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.22 g, 0.54 mmol, 71%). ^{1}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. for $C_{23}H_{28}N_4OS$ $(M+H)^+$: 409.3; found: 409.2.

Example 97.

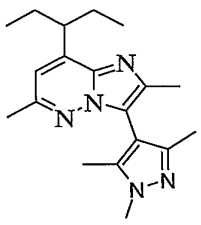
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrimidin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



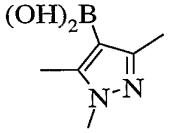
A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 2-tributylstannanyl-pyrimidine (0.34 g, 0.92 mmol) and THF (5 mL) is de-gassed with N_2 for 10 minutes Triphenylarsine (0.047 g, 0.15 mmol) and $Pd_2(dba)_3$ (0.035 g, 0.038 mmol) is added and the solution heated at 55°C for 48 hours and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient), dissolved in acetonitrile (20 mL), washed with hexane (3 x 20 mL) and concentrated to furnished the title compound (0.097 g, 0.25 mmol, 32%). ^{1}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. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 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) of 4-bromo-1,3,5-trimethyl pyrazole to 4.0 ml THF. The mixture is cooled to -78^0C and 1eq of n-BuLi (1.6 M) is added via syringe. The mixture is stirred 1.5 hrs, and 0.19ml of trimethylborate (1.08 eq) is added. The reaction mixture is stirred 2 hrs, allowing bath to reach -10^0C, then 1.5 ml of 5N HCl is added and stirred 30 minutes longer. The aqueous layer is extracted 3 times with ethyl acetate. The combined organics are dried over MgSO4, filtered, and evaporated to an oil. The oil is dissolved in methanol/methylene chloride and re-evaporated. The residue is triturated with acetone/ethyl acetate then filtered to obtain title compound as a white solid 92.1 mg (37.6%). ^{1}H-NMR (DMSO-d_6): δ5.92 (s); 3.72 (s, 3H); 2.34 (s, 3H); 2.26 (s, 3H) ppm.

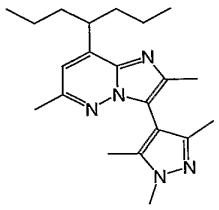
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.

3-Iodo-2,6-dimethyl-8-(1-ethyl-propyl)-imidazo[*1,2-b*]pyridazine (200mg, 0.582 mmol), 1,3,5-trimethylpyrazole-4-boronic acid (233mg, 1.53 mmol), Pd(PPh3)4 (13.4mg, 0.01 mmol) are combined in a microwave pressure tube. Then 0.58 ml of 2N Na2CO3 and 3.0ml of dimethoxyethane/H20/ethanol (7:3:2) solution is added. The mixture is microwaved at 155^0C for 20minutes. Water is added and the mixture is extracted four times with ethyl acetate. The combined organics are dried over MgSO4, filtered, then

evaporated to a residue which is chromatographed using hexanes, then 1:1 hexanes: ethyl acetate, then 100% ethyl acetate to give the title compound (6.4%) as a yellow oil. ^{1}H-NMR (DMSO-d_6): δ6.86 (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.

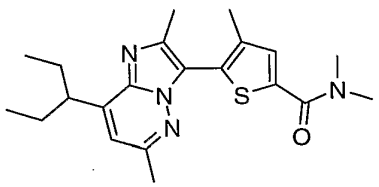
Preparation of 2,6-Dimethyl-8-(1-propyl-butyl)-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.



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 5.0mg (0.0004 mmol) of Pd(PPh3)4 are combined in microwave pressure vessel with 1.5ml of dimethylether/H2O/ethanol (7:3:2) solution. The mixture is microwaved at 140^{0}C for 25 minutes. The mixture is evaporated and chromatographed on silica gel column using hexanes then 3:1 hexane:ethyl acetate, then 1:1 hexane:ethyl acetate to give the title compound (22.8%) as a clear oil. ^{1}H-NMR (DMSO-d_6): δ6.88 (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); 1.60-1.76 (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.

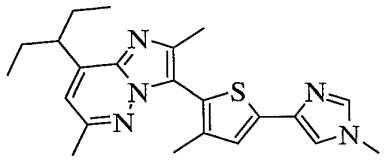
Preparation of 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid dimethylamide.



Using a procedure analogous to Example 23 B, 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid (151 mg, 0.42 mmol) and 2.0 M dimethylamine (2.0 mL, 4 mmol) give the title compound (161 mg, 0.42 mmol, 100%). 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), 7.30 (s, 1H). ES-MS (m/z): calcd for C21H28N4OS (M+H)+: 385.6 found: 385.3.

Example 101.

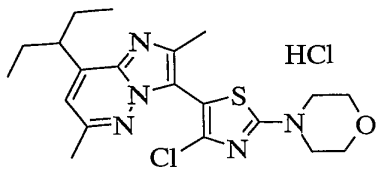
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-Imidazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31. from 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 $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 3-iodo-1-methyl-*1H*-imidazole (0.24 mL, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.030g, 0.076 mmol, 8%). ^{1}H NMR ($CDCl_3$), 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), 6.66 (s, 1H), 7.09 (d, *J* = 1.3 Hz, 1H), 7.19 (s, 1H), 7.86 (d, *J* = 1.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.2; found: 394.2.

Example 102.

Preparation of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine, hydrochloride salt.

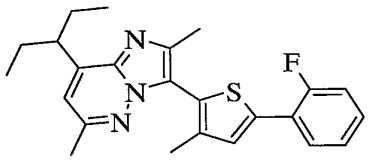


IPA (225.0 mL) is added to compound N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (18.8 g, 0.0448 mmol,

below) in a 1 L 1-neck round-bottomed flask The starting material slurry is heated to 50 °C on a Buchi bath, at which time a hazy solution resulted. Concentrated (12 M) aqueous HCl (3.73 mL, 0.0448 mmole, 1.0 eq) is added all at once, and the hazy solution is stirred at 50 °C on the Buchi for 10 minutes, then evaporated to a yellow solid under vacuum. After 20 minutes at room temperature under vacuum (weight of 20.9 g), acetone (100 mL) is added and the resulting yellow slurry is stirred at room temperature for 1 hour, then cooled with an ice bath and stirred for an additional 1 hour. The slurry is filtered, rinsed with acetone, and dried overnight under vacuum at 40°C to provide pale yellow-white crystalline solid 19.18 g (94%). ^{1}H NMR (DMSO): δ 7.52 (s, 1H), 3.73 (t, J = 4.6, 4H), 3.49 (t, J = 5.2 Hz, 4H), 3.39 (m, 1H), 2.57 (s, 3H), 2.49 (s, 3H), 1.77 (m, 4H), 0.80 (t, J = 7.4 Hz, 6H).

Example 103.

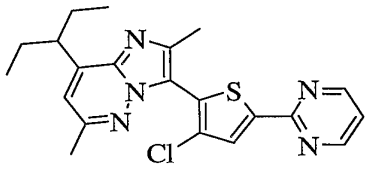
Preparation of 8-(1-ethyl-propyl)-3-[5-(2-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 30 B, 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, 0.65 mmol), and 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), *n*-PrOH (2 mL), and $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol) furnish the title compound (0.022 g, 0.054 mmol, 11%). ^{1}H NMR ($CDCl_3$), 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* = 7.8, 1.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.2; found: 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.

To a –78 °C solution of 3-(3-chloro-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) is added 1.6 M *n*-BuLi (4.1 mL). After 30 minutes $B(OMe)_3$ (0.74 mL, 6.59 mmol) is added, the solution is warmed to ambient temperature and stirred overnight. 1 M HCl (30 mL) is added and the solution stirred for 20 minutes. The solution is made basic with 5 M NaOH. The organic layer is extracted with 1 M NaOH (30 mL). The combined aqueous layers are made acidic with 5 M HCl, K_3PO_4•3 H_2O is added and the PH adjusted to 5.5 using 1 M NaOH. The combined aqueous layers are extracted with EtOAc (200 mL), washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (2.20 g, 5.82 mmol, 97%). LC/MS (m/z): calcd. for $C_{17}H_{21}BClN_3O_2S$ $(M+H)^+$: 378.7; found: 378.0.

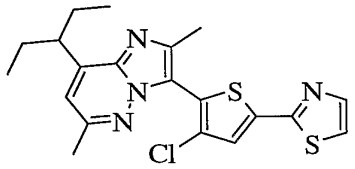
B. 3-(3-Chloro-5-pyrimidin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), and *i*-PrOH (3 mL) are degassed with N_2 for 15 minutes. $Pd(OAc)_2$ (7.4 mg, 0.033 mmol) and PPh_3 (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% Na_2CO_3 (35 mL), brine (35 mL), dried over Na_2SO_4, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.077 g, 0.19 mmol, 29%). ^1H NMR ($CDCl_3$) 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), 7.16 (t, J = 5.0 Hz, 1H), 8.00 (s, 1H), 8.74 (d, J = 5.0 Hz, 2H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 412.2.

Example 105.

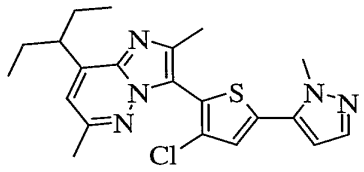
Preparation of 3-(3-chloro-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to 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, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) and *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.099 g, 0.24 mmol, 35%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (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. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 417.1; found: 417.1.

Example 106.

Preparation of 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.

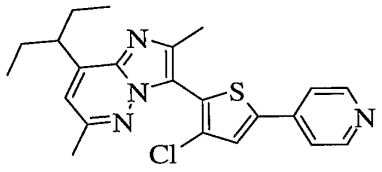


To a –78 °C solution of 1-methyl-*1H*-pyrazole (0.12 g, 1.45 mmol) and THF (4 mL) is added 1.6 M *n*-BuLi (0.91 mL, 1.45 mmol). After 45 minutes 0.5 M $ZnCl_2$ (2.9 mL, 1.45 mmol) is added and the solution is warmed to ambient temperature. After 30 minutes 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example Rupp-88) (0.30 g, 0.73 mmol) and $PdCl_2$(dppf) (0.027

g, 0.036 mmol) are added and the solution heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.15 g, 0.36 mmol, 50%). ^1H NMR ($CDCl_3$) δ 0.88 (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. for $C_{21}H_{24}ClN_5S$ $(M+H)^+$: 414.2; found: 414.2.

Example 107.

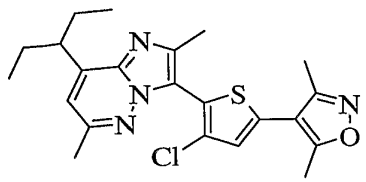
Preparation of 3-(3-chloro-5-pyridin-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to 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, 0.66 mmol), 4-bromo-pyridine hydrochloride (0.26 g, 1.32 mmol), 2 M Na_2CO_3 (1.00 mL, 1.99 mmol), *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.16 g, 0.59 mmol, 59%). ^1H NMR ($CDCl_3$) δ 0.87 (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. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.1; found: 411.1.

Example 108.

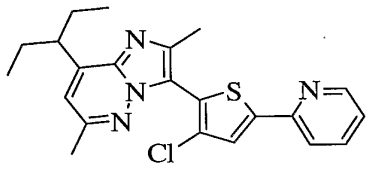
Preparation of 3-[3-chloro-5-(3,5-dimethyl-isoxazol-4-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to 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, 0.66 mmol), 4-iodo-3,5-dimethyl-isoxazole (0.30 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) and *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.14 g, 0.50 mmol, 50%). ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.43 (s, 3H), 2.53 (s, 6H), 2.57 (s, 3H), 3.27-3.38 (m, 1H), 6.71 (s, 1H), 7.01 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}ClN_4OS$ $(M+H)^+$: 429.2; found: 429.2.

Example 109.

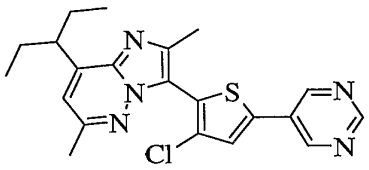
Preparation of 3-(3-chloro-5-pyridin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 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 $PdCl_2$(dppf) (0.022 g, 0.030 mmol) is added a 0.5 M solution of 2-pyridylzinc bromide (2.40 mL, 1.21 mmol) and the solution heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) followed by recrystallization from CH_3CN furnish the title compound (0.15 g, 0.36 mmol, 60%). ^{1}H NMR ($CDCl_3$) δ 0.88 (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): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 412.0; found: 412.4.

Example 110.

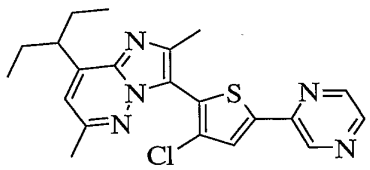
Preparation of 3-(3-chloro-5-pyrimidin-5-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to 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, 0.66 mmol), 4-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.053 g, 0.13 mmol, 20%). ^1H NMR ($CDCl_3$) δ 0.88 (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. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 411.2.

Example 111.

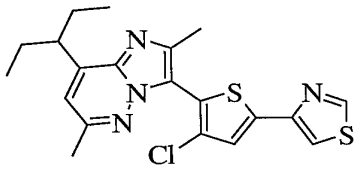
Preparation of 3-(3-chloro-5-pyrazin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.40g, 1.06 mmol), 2-iodo-pyrazine (0.16 g, 1.59 mmol), 2 M Na_2CO_3 (1.06 mL, 2.12 mmol) and *i*-PrOH (5 mL), $Pd(OAc)_2$ (0.012 g, 0.053 mmol), and PPh_3 (0.042 g, 0.16 mmol) furnish the title compound (0.15 g, 0.36 mmol, 34%). ^1H NMR ($CDCl_3$) δ 0.87 (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): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 412.3.

Example 112.

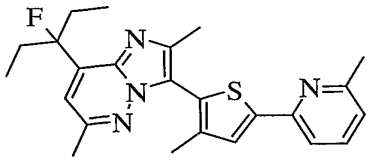
Preparation of 3-(3-chloro-5-thiazol-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a 0 °C solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.45 mmol) and THF (2 mL) is added 0.05 g/mL of Reike® Zn (3.80 mL, 2.91 mmol). The solution is heated at a reflux for 1 hour, and the excess Zn allowed to settle for 1 hour at ambient temperature. The solution is transferred to a flask of 4-bromo-thiazole (Kelly, T. et al. *Tetrahedron Lett.* 1995, 51, 9293) (0.29 g, 1.74 mmol). $PdCl_2(dppf)$ (0.027 g, 0.036 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (40 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) followed by ISCO column chromatography (100% Et_2O) to furnish the title compound (0.098 g, 0.24 mmol, 16%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (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. for $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; found: 417.3.

Example 113.

Preparation of 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.

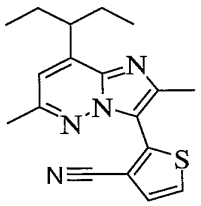


To a –78 °C solution of 3-{2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol (0.23 g, 0.55 mmol) and CH_2Cl_2 (3 mL) is added a solution of [bis(2-methoxyethyl)amino]sulfur triflouride (0.14 g, 0.60 mmol) and CH_2Cl_2 (2 mL). The solution is warmed to ambient temperature and

stirred overnight. The solution is washed with sat. $NaHCO_3$ (5 mL) and concentrated. The reside is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.13g, 0.31 mmol, 57%). ^1H NMR ($CDCl_3$) δ 0.80 (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. for $C_{24}H_{27}FN_4S$ $(M+H)^+$: 423.2; found: 423.4.

Example 114.

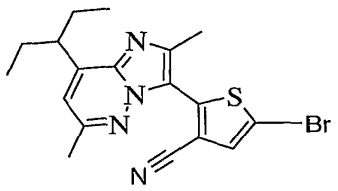
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile.



To a solution 0.05 g/mL of Reike® Zn (31 mL, 23.93 mmol) is added 2-bromo-thiophene-3-carbonitrile (Fournari, P. et al. Bull. Soc. Chim. Fr., 1967, 4115) (2.25 g, 11.96 mmol) and THF (5 mL). The solution is heated at a reflux for 2 hours, cooled to ambient temperature and the excess Zn allowed to settle. The solution is transferred via a cannula into a flask of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.5 g, 7.98 mmol) and $PdCl_2$(dppf) (0.29 g, 0.040 mmol). The mixture is heated at 65°C overnight, diluted with EtOAc (75 mL), washed with sat. NH_4Cl (2 x 75 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-20% EtOAc/hexane gradient) furnish the title compound (1.10 g, 3.39 mmol, 42%). ^1H NMR ($CDCl_3$) 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): calcd. for $C_{18}H_{20}N_4S$ $(M+H)^+$: 325.5; found: 325.2.

Example 115.

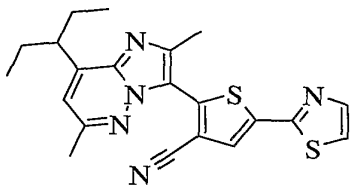
Preparation of 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile.



To a solution of 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 CH_2Cl_2 (10 mL) is added NBS (0.48 g, 2.69 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated to furnish the title compound (1.03 g, 2.55 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.56 (s, 3 H), 2.60 (s, 3H), 3.24-3.32 (m, 1H), 6.76 (s, 1H), 7.30 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{19}BrN_4S$ $(M+H)^+$: 404.4; found: 404.1.

Example 116.

Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile.

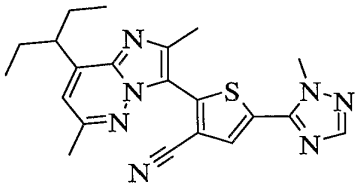


To a flask containing 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.023 g, 0.031 mmol) is added a solution of 0.5 M 2-thiazolylzinc bromide (6.0 mL, 3.10 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.16 g, 0.39 mmol, 64%). ^{1}H NMR ($CDCl_3$) 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), 6.78 (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. for $C_{21}H_{21}N_5S_2$ $(M+H)^+$: 408.6; found: 408.1.

Example 117.

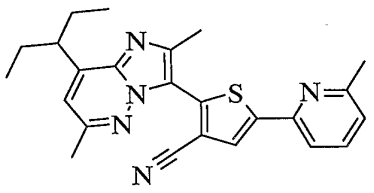
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile.



To a –78 °C solution of 1-methyl-1,2,4-triazole (0.14 mL, 1.86 mmol) and THF (5 mL) is added a 1.6 M solution of *n*-BuLi in hexanes (1.20 mL, 1.86 mmol) after 30 minutes a 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature and stirred for 30 minute. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (example Rupp-122) (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.023 g, 0.031 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-60% EtOAc/hexane gradient), and is chromatographed (50 x 250 C18 X-Terra RP column, 30-90% 10 mM NH_4HCO_3/water/5 % ACN: ACN gradient). The residue is dissolved in Et_2O (25 mL), washed with sat. $NaHCO_3$ (25 mL), dried over MgSO4, filtered and concentrated to furnish the title compound (0.013 g, 0.032 mmol, 5%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3 H), 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): calcd. for $C_{21}H_{23}N_7S$ $(M+H)^+$: 406.5; found: 406.2.

Example 118.

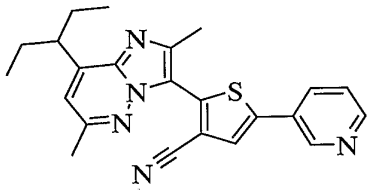
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-(6-methyl-pyridin-2-yl)-thiophene-3-carbonitrile.



To a flask containing 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 $PdCl_2$(dppf) (0.024 g, 0.033 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.50 mL, 1.24 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-25% EtOAc/hexane gradient), furnish the title compound (0.11 g, 0.26 mmol, 39%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.76-1.92 (m, 4H), 2.57 (s, 3 H), 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. for $C_{24}H_{25}N_5S$ $(M+H)^+$: 416.6; found: 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.

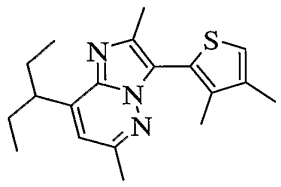


To a –78 °C solution of 3-iodo-pyridine (0.32 g, 1.56 mmol), 0.5 M $ZnCl_2$ in THF (3.20 mL, 1.59 mmol), and THF (2 mL) is added 1.7 M *t*-BuLi (1.85 mL, 3.15 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.21 g, 0.52 mmol) and $Pd(PPh_3)_4$ (0.03 g, 0.026 mmol) are added and the solution

heated at 55 °C for 1 hour, cooled to ambient temperature and stirred overnight, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (2 x 40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-40% EtOAc/hexane gradient), furnish the title compound (0.15 g, 0.37 mmol, 71%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.58 (s, 3 H), 2.66 (s, 3H), 3.26-3.35 (m, 1H), 6.78 (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. for $C_{23}H_{23}N_5S$ $(M+H)^+$: 402.6; found: 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-Bromo-3,4-dimethyl-thiophene.

To a solution of 3,4-dimethyl-thiophene (2.0 g, 17.82 mmol) (Minato et. al., *Tetrahedron* 1982, 38, 3347) in CH_2Cl_2 (20 mL) is added NBS (3.3 g, 18.72 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated. The residue is purified by ISCO column chromatography (100% hexane) furnish the title compound (3.0 g, 16.70 mmol). ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.17 (s, 3H), 6.85 (s, 1H).

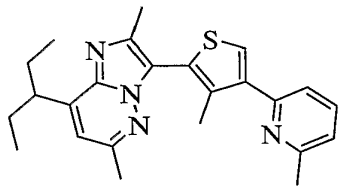
B. 3-(3,4-Dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3,4,3',4'-tetramethyl-[2,2']bithiophenyl-5-yl)-imidazo[*1,2-b*]pyridazine, respectively.

To a solution of 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 Cs_2CO_3 (7.24 g, 22.23 mmol) and DMF (50 mL) is de-gassed with N_2 for 20 minutes. $Pd_2(dba)_3$ (0.48 g, 0.053 mmol) and PPh_3 (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 x

200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated. The residue is purified by ISCO column chromatography (10% -15% EtOAc/hexane gradient) furnish 2.04 g of a brown oil which is chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1 % TFA /ACN gradient) furnish the title compound (0.41 g, 1.25 mmol, 12%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.94 (m, 4H), 2.00 (s, 3 H), 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): calcd. for $C_{19}H_{25}N_3S$ $(M+H)^+$: 328.5; found: 328.3.

Example 121.

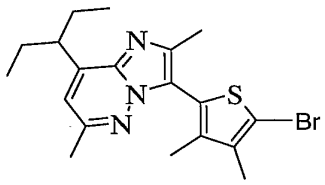
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-4-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



To a flask containing 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 $PdCl_2$(dppf) (0.023 g, 0.032 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.5 mL, 1.27 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-20% EtOAc gradient) and is chromatographed (50 x 250 C18 Symmetry column, 10-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient). The residue is dissolved in Et_2O (20 mL), washed with sat. $NaHCO_3$ (15 mL) dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.066 g, 1.57 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.20 (s, 3 H), 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. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; found: 405.3.

Example 122.

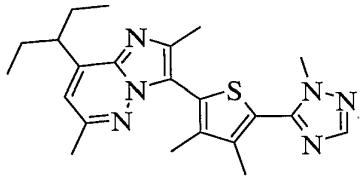
Preparation of 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 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 CH_2Cl_2 (30 mL) is added NBS (0.23 g, 1.32 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated to furnish the title compound (0.41 g, 1.01 mmol, 80%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 6H), 1.72-1.94 (m, 4H), 2.02 (s, 3 H), 2.18 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.67 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{24}BrN_3S$ $(M+H)^+$: 407.4; found: 407.3.

Example 123.

Preparation of 3-[3,4-dimethyl-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.

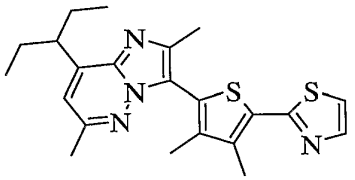


To a –78 °C solution of 1-methyl-1,2,4-triazole (0.056 mL, 0.74 mmol) and THF (2 mL) is added a 1.6 M solution of *n*-BuLi in hexanes (0.46 mL, 0.74 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. The solution is cooled to 0 °C, a 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature and stirred for 30 minute. 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 $PdCl_2$(dppf) (0.009 g, 0.012 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried

over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-60% EtOAc/hexane gradient), followed by a second purification by ISCO column chromatography (100% Et_2O) furnish the title compound (0.07 g, 0.17 mmol, 70%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3 H), 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. for $C_{22}H_{28}N_6S$ $(M+H)^+$: 409.6; found: 409.2.

Example 124.

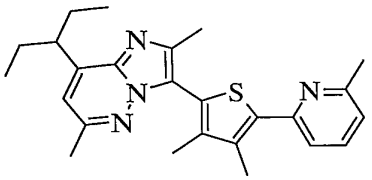
Preparation of 3-(3,4-dimethyl-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 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 minutes and 0.5 M $ZnCl_2$ in THF (0.52 mL, 0.26 mmol) is added. The solution is warmed to ambient temperature and stirred for 30 minutes. 2-Bromo-thiazole (0.044 mL, 0.49 mmol), and $PdCl_2$(dppf) (0.009 g, 0.012 mmol) are added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient), furnish the title compound (6.1 mg, 0.015 mmol, 6%). ^1H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.49 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.29-3.39 (m, 1H), 6.68 (s, 1H), 7.35 (d, J = 3.1 Hz, 1H), 7.86 (d, J = 3.1 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{26}N_4S_2$ $(M+H)^+$: 411.6; found: 411.2.

Example 125.

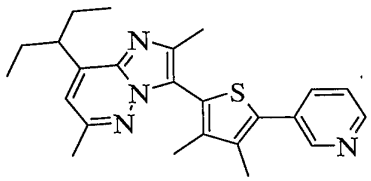
Preparation of 3-[3,4-dimethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 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 $PdCl_2$(dppf) (9 mg, 0.012 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (0.98 mL, 0.49 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.029 g, 0.069 mmol, 29%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.04 (s, 3 H), 2.45 (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. for $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.6; found: 419.4.

Example 126.

Preparation of 3-[3,4-dimethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

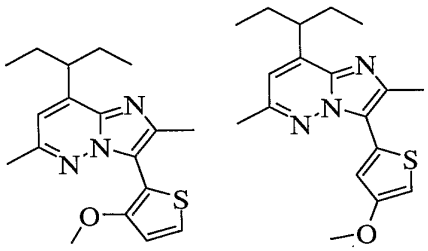


To a –78 °C solution of 3-iodo-pyridine (0.15 g, 0.74 mmol) and 0.5 M $ZnCl_2$ in THF (1.5 mL, 0.75 mmol) is added *t*-BuLi (0.88 mL, 1.49 mmol). The slurry is warmed to ambient temperature and stirred for 30 minutes. 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol) are added and the solution stirred at ambient

temperature for 2 days, diluted with EtOAc (35 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (6.1 mg, 0.015 mmol, 6%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.29 (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. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.6; found: 405.2.

Example 127 & 128.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-3-(4-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Ex. 127. Ex. 128.

To a solution of 3-methoxy-thiophene (2.19 g, 19.14 mmol) in Et_2O (50 mL) is added 1.6 M *n*-BuLi (12.20 mL, 19.46 mmol). The solution is heated at a reflux for 30 minutes and cooled to ambient temperature. As solution of 0.5 M $ZnCl_2$ (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, 6.38 mmol) and $PdCl_2$(dppf) (0.23 g, 0.032 mmol) are added and the solution is heated at 65 °C for 4 hours, diluted with EtOAc (250 mL), washed with sat. NH_4Cl (250 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-25% EtOAc/hexane gradient) furnish the title compounds (1.50 g, 4.55 mmol, 71%) and (0.23 g, 0.70 mmol, 11%), respectively.

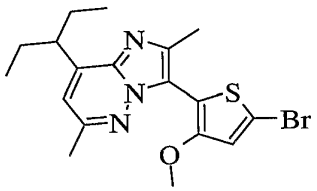
Example 127: ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.59 (s, 3H), 2.70 (s, 3H), 3.26-3.35 (m, 1H), 3.86 (s, 3H), 6.32 (d, J = 1.6 Hz, 1H), 6.67 (s, 1H),

7.41 (d, J = 1.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; found: 330.3.

Example 128: ^1H NMR ($CDCl_3$) 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. for $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; found: 330.3.

Example 129.

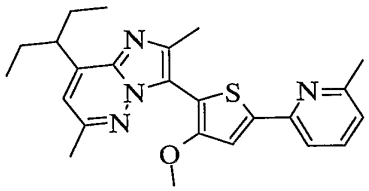
Preparation of 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 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 CH_2Cl_2 (10 mL) is added NBS (0.44 g, 2.49 mmol). The solution is stirred for 1 hour, washed with water (3 x 10 mL), concentrated and purified by ISCO column chromatography (5%-15% EtOAc/hexane gradient) to furnish the title compound (0.87 g, 2.13 mmol, 90%). ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.82 (s, 3H), 6.65 (s, 1H), 6.97 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3OS$ $(M+H)^+$: 408.1; found: 408.3.

Example 130.

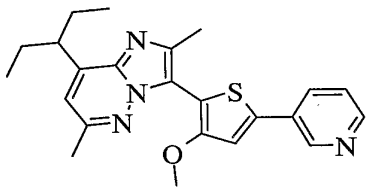
Preparation of 8-(1-ethyl-propyl)-3-[3-methoxy-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.49 mmol) and $PdCl_2$(dppf) (0.018 g, 0.024 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.47 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.066 g, 1.57 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.50 (s, 3 H), 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. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.6; found: 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.

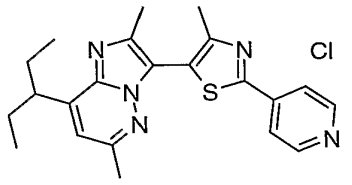


To a –78 °C solution of 3-iodo-pyridine (0.32 g, 1.56 mmol) and 0.5 M $ZnCl_2$ in THF (3.20 mL, 1.59 mmol) is added *t*-BuLi (2.27 mL, 3.85 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.26 g, 0.64 mmol) and $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) are added and the solution heated at 50 °C for 1 hour, cooled to ambient temperature and stirred overnight. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-50% EtOAc/hexane gradient), furnish the title compound (0.16 g, 0.39 mmol, 61%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 3 H), 2.55 (s, 3H), 3.28-3.38 (m, 1H), 3.93, (3H), 6.67 (s, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.31-7.36 (m, 1H), 7.88-

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. for $C_{23}H_{26}N_4OS$ $(M+H)^+$: 407.6; found: 407.4.

Example 132.

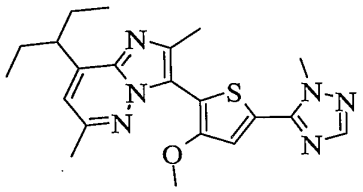
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-4-yl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine, hydrochloride salt.



A mixture of 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), $Pd(PPh_3)_4$ (100 mg, 0.08 mmol), toluene (2 mL), MeOH (1mL), and K_2CO_3 (2 M aqueous solution, 3.5mL) is heated at 100 °C for 18 hours. Ethyl acetate (20mL) 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 hexanes and ethyl acetate to obtain the free amine of the title compound (200 mg, 40%). The purified product is dissolved in 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 ^{1}H-NMR ($CDCl_3$), δ 8.2 (m, 2H); 7.05 (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.

Preparation of 8-(1-ethyl-propyl)-3-[3-methoxy-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-1-methyl-1*H*-[1,2,4]triazole.

To a –78 °C solution of 1-methyl-*1H*-[1,2,4]triazole (1.0 mL, 13.20 mmol) and THF (100 mL) is added 1.6 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, 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 $MgSO_4$, filtered and concentrated to furnish the title compound (1.37 g, 8.46 mmol, 64%). ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). LC/MS (m/z): calcd. for $C_3H_4BrN_3$ $(M+H)^+$: 162.0; found: 161.9.

B. 8-(1-Ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 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 CH_3CN (10 mL) is added NIS (0.54 g, 2.39 mmol). The solution is stirred overnight, concentrated, diluted with EtOAc (30 mL), washed with water (30 mL), sat. NH_4Cl (30 mL), 20% ($NaHSO_3$) (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.91 g, 2.00 mmol, 88%). ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.83 (s, 3H), 6.64 (s, 1H), 7.12 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}IN_3OS$ $(M+H)^+$: 456.4; found: 456.0.

C. 5-Bromo-1-methyl-1*H*-[1,2,4]triazole.

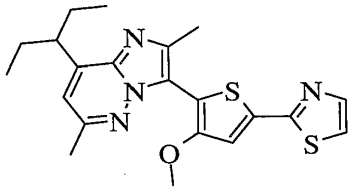
To a –78 °C solution of 1-methyl-1*H*-[1,2,4]triazole (1.0 mL, 13.20 mmol) and THF (100 mL) is added 1.6 M *n*-BuLi (8.70 mL, 13.86 mmol). After 45 minutes 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added, the solution warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.37 g, 8.46 mmol, 64%). ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). LC/MS (m/z): calcd. for $C_3H_4BrN_3$ $(M+H)^+$: 162.0; found: 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-dimethyl-imidazo[*1,2-b*]pyridazine.

To a slurry of 0.05 g/ mL of Reike® Zn in THF (2.8 mL, 2.11 mmol) is added 5-bromo-1-methyl-*1H*-[1,2,4]triazole and THF (2 mL). The solution is heated at 65 °C for 1 hour, cooled to ambient temperature and the excess Zn allowed to settle for 1 hour. The solution is transferred to a flask containing 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 $Pd(PPh_3)_4$ (0.041 g, 0.035 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL) washed with sat. NH_4Cl (30 mL). The aqueous phase is extracted with EtOAc (20 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The reside is purified by ISCO column chromatography (20%-65% EtOAc/hexane gradient) followed by ISCO column chromatography (100% Et_2O) furnish the title compound (0.19 g, 0.46 mmol, 62%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.51 (s, 3 H), 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): calcd. for $C_{21}H_{26}N_6OS$ $(M+H)^+$: 411.5; found: 411.3.

Example 134.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-5-thiazol-2-yl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

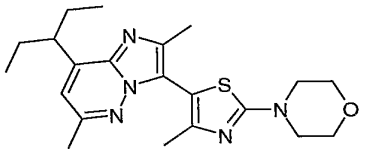


To a flask containing 8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.45 g, 0.99 mmol) and $PdCl_2$(dppf) (0.057 g, 0.078 mmol) is added a 0.5 M solution of 2-thiazolylzinc bromide (9.9 mL, 4.94 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.29 g, 0.70 mmol, 71%). ^1H NMR ($CDCl_3$) 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. for $C_{21}H_{24}N_4OS_2$ $(M+H)^+$: 413.6; found: 414.3.

Example 135.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-morpholin-4-yl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine.



110 mg of 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) are dissolved in 3.0 ml of THF and 182 mg of cesium carbonate (0.56 mmol) is added. The mixture is put in 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 give 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=4.8Hz), 3.56(t, 4H, J=4.8Hz), 3.35(m, 1H) 2.56(s, 3H), 2.46(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.6Hz)

The following compounds are prepared essentially as described in Example 135. with 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and the named amine:

Ex	Name	Amine	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
136.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine	2M Methyl-amine/THF	6.71 (s, 1H), 5.44 (s, NH), 3.35 (m, 1H), 3.06 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.6 Hz, 6H).	344
137.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dimethylamine	2M Dimethyl-amine/THF	6.70 (s, 1H), 3.36 (m, 1H), 3.17 (s, 6H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	358
138.	N-Ethyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine	N-Methyl-ethylamine	6.70 (s, 1H), 3.59 (q, J = 7.6 Hz, 2H), 3.37 (m, 1H), 3.15 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.5 Hz, 2H), 0.90 (t, J = 7.1 Hz, 6H).	372
139.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-diethylamine	Diethyl-amine	6.71 (s, 1H), 3.56 (q, J = 7.1 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.3 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	386

140.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(furan-2-ylmethyl)-methylamine	N-Methyl-(furan-2-yl)-methyl-amine	7.44 (s, 1H), 6.69 (s, 1H), 6.38 (s, 2H), 4.72 (s, 2H), 3.36 (m, 1H), 3.14 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).	424
141.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl}thiomorpholine	Thio-morpholine	6.71 (s, 1H), 3.92 (m, 4H), 3.37 (m, 1H), 2.80 (m, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	416
142	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methoxy-ethyl)-amine	2-methoxy-ethylamine	6.71 (s, 1H), 5.90 (s, NH), 3.66 (t, J = 5.4 Hz, 2H), 3.56 (t, J = 4.6 Hz, 2H), 3.44 (s, 3H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	388
143	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isopropyl-amine	i-propyl-amine	6.69 (s, 1H), 5.15 (s, NH), 3.74 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 1.35 (d, J = 5.4 Hz, 6H), 0.90 (t, J = 7.4 Hz, 6H).	372
144.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-pyrrolidine	Pyrrolidine	6.68 (s, 1H), 3.55 (m, 4H), 3.36(m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 2.09 (m, 4H), 1.86 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).	384

145.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	n-propyl-amine	6.70 (s, 1H), 5.21 (s, NH), 3.39 (t, J = 7.2 Hz, 2H), 3.29 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.85 (m, 4H), 1.74 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.4 Hz, 6H).	372
146	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-benzylamine	Benzyl-amine	7.47-7.23 (m, 5H), 6.70 (s, 1H), 5.52 (s, NH), 6.70 (s, 2H), 3.34 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H).	420
147	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(2-methoxy-ethyl)-ethylamine	N-(2-Methoxy-ethyl)-ethylamine		416
148	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methoxy-ethyl)-n-propylamine	N-(2-meth-oxyethyl)-n-propyl-amine	6.69 (s, 1H), 3.72 (m, 4H), 3.47 (t, J = 7.4 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.87 (m, 6H), 0.99 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	430
149	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidine	piperidine	6.68 (s, 1H), 3.53 (t, J = 4.7 Hz, 4H), 3.36 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.86 (m, 4H), 1.71 (m, 6H), 0.90 (t, J = 7.4 Hz,	398

			6H).	
150	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-3-pentylamine	3-amino-pentane	6.70 (s, 1H), 5.24 (s, NH), 3.32 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 1.94 (s, 3H), 1.85 (m, 4H), 1.72 (m, 2H), 1.60 (m, 2H), 1.02 (t, J = 7.5 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	400
151	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-cyclo-propylamine	Cyclo-propylamine	6.70 (s, 1H), 6.51 (s, NH), 3.35 (m, 1H), 2.67 (m, 1H), 2.57(s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H), 0.82 (m, 2H), 0.77 (m, 2H).	370
152	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-allylamine	Allylamine	6.70 (s, 1H), 6.0 (m, 1H), 5.60 (s, NH), 5.38 (dd, J = 1.3, 17.4 Hz, 1H), 5.27 (dd, J = 1.2, 10.3 Hz, 1H), 4.0 (d, J = 5.2 Hz, 2H), 3.45 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 6.8 Hz, 6H).	370
153	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,2,3,6-tetra-hydro-pyridine	1,2,3,6-tetra-hydro-pyridine	6.70 (s, 1H), 5.96 (m, 1H), 5.81 (m, 1H), 4.02 (t, J = 3.1 Hz, 2H), 3.72 (t, J = 5.5 Hz, 2H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.35 (m, 2H), 2.19 (s, 3H), 1.87 (m,	396

			4H), 0.90 (t, J = 7.4 Hz, 6H).	
154	N-Ethyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	N-ethyl-n-propyl-amine	6.69 (s, 1H), 3.58 (q, J = 7.1 Hz, 2H), 3.43 (t, J = 7.5 Hz, 2H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.80 (m, 4H), 1.30 (t, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	400
155	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	N-methyl-n-propyl-amine	6.68 (s, 1H), 3.46 (t, J = 8.3 Hz, 2H), 3.35 (m, 1H), 3.16 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.80 (m, 2H), 1.00 (t, J = 7.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	386
156	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isopropyl-amine	N-Methyl-2-propyl-amine	6.70 (s, 1H), 4.40 (m, 1H), 3.36 (m, 1H), 2.99 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.29 (d, J = 6.4 Hz, 6H), 0.90 (t, J = 7.1 Hz, 6H).	386
157	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-2-propyn-1-amine	N-Methyl-2-Propyn-1-amine	6.70 (s, 1H), 4.40 (d, J = 2.5 Hz, 2H), 3.35 (m, 1H), 3.17 (s, 3H), 2.56 (s, 3H), 2.45 (s, 3H), 2.34 (m, 1H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	382

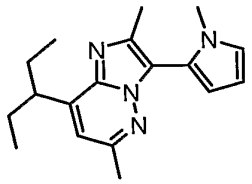
158	N-Methyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-3-amino-propionitrile	N-Methyl-3-amino-propio-nitrile	6.71 (s, 1H), 3.92 (t, J = 6.4 Hz, 2H), 3.37 (m, 1H), 3.25 (s, 3H), 2.9 (t, J = 6.4 Hz, 2H), 2.58 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).	397
159	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- cyclopropyl-methylamine	Cyclo-propyl-methyl-amine	6.68 (s, 1H), 5.35 (s, NH), 3.34 (m, 1H), 3.19 (t, J = 6.3 Hz, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 2.16 (s, 3H), 1.86 (m, 4H), 1.19 (m, 1H), 0.91 (t, J = 7.1 Hz, 6H), 0.61 (m, 2H), 0.31 (m, 2H).	384
160	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methylsulfanyl)-ethylamine	2-methyl-sulfanyl-ethylamine	6.72 (s, 1H), 5.58 (s, NH), 3.58 (m, 2H), 3.35 (m, J = 7.3, 14.4, 1H), 2.85 (m, 2H), 2.57 (s, 3H), 2.46 (s, 3H), 2.17 (s, 6H), 1.85 (m, 4H), 0.90 (t, J = 6.7 Hz, 6H).	404
161	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- N-{[1,3]dioxolan-2-ylmethyl-methylamine	N-{[1,3]di-oxolan-2-yl-methyl}-methyl-amine	6.72 (s, 1H), 5.22 (m, 1H), 4.05 (m, 2H), 3.94 (m, 2H), 3.73 (d, J = 4.5 Hz, 2H), 3.35 (m, J = 6.6, 14.1 Hz, 1H), 3.23 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).	430
162	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-	N-Methyl-2-propen-1-yl-amine	6.71 (s, 1H), 5.93 (m, 2H), 5.30 (m, 2H), 4.16 (d, J = 5.9 Hz, 2H), 3.39 (m, 1H),	384

	3-yl]-4-methyl-thiazol-2-yl}- N-Methyl-2-propen-1-yl-amine		3.12 (s, 3H), 2.58 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).	
163	(R)-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(tetrahydro-furan-2-ylmethyl)-amine	(R)-(tetrahydro-furan-2-ylmethyl)-amine	6.70 (s, 1H), 5.44 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 2H), 0.90 (t, J = 7.3 Hz, 6H).	414
164	(S)-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(tetrahydro-furan-2-ylmethyl)-amine	(S)-(tetrahydro-furan-2-ylmethyl)-amine	6.69 (s, 1H), 5.45 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.59 (m, 1H), 3.34 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 1H), 0.90 (t, J = 7.2 Hz, 6H).	414
165	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(2-methoxyethyl)-methylamine	N-Methyl-2-methoxy-ethyl-amine	6.70 (s, 1H), 3.74 (t, J = 4.2 Hz, 2H), 3.71 (t, J = 4.1 Hz, 2H), 3.43 (s, 3H), 3.37 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	402
166	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-	N-Methyl-benzyl-amine	7.43-7.32 (m, 5H), 6.69 (s, 1H), 4.76 (s, 2H), 3.35 (m, 1H), 3.10 (s, 3H), 2.57(s, 3H), 2.48 (s, 3H), 2.21 (s,	434

	yl}-N-methyl-benzylamine		3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).	
167	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-ethyl-benzylamine	N-Ethyl-benzyl-amine	7.41-7.31 (m, 5H), 6.68 (s, 1H), 4.76 (s, 2H), 3.54 (q, J = 7.3, 2H), 3.36 (m, 1H), 2.56(s, 3H), 2.49 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	448
168	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(1-methoxy-2-butyl)-amine	1-Methoxy-2-amino-butane		416
169	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methyl-isobutylamine	N,2-Di-methyl- n-propyl-amine		400
170	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isobutyl-amine	2-Methyl-n-propyl-amine		386

Example 171.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-^1H-pyrrol-2-yl)-imidazo[*1,2-b*]pyridazine.



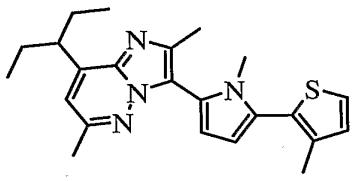
A THF solution (10 mL) of N-methylpyrrole (Aldrich, 800 μL, 9.0 mmol) is cooled to -78 °C under N_2 then treated with *tert*-BuLi (1.7 M in pentane, 5.3 mL, 9.0 mmol). The solution is warmed to room temperature for 30 minutes then cooled to -78 °C and treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 18 mL, 9.0 mmol). The resulting mixture is warmed to room temperature and treated with a THF slurry (5 mL) containing 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.02 gm, 3.0 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 140 mg, 0.17 mmol). The mixture is heated to 60 °C overnight, then poured into sat'd aq NH_4Cl (50 mL) and extracted with diethyl ether (75 mL). The organic extract is ished with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (407.5 mg, 46% yield) as an oil.

ES-MS (m/z): calc'd for $C_{18}H_{24}N_4$: 296.20; found 297.5 $(M+H)^+$

^{1}H NMR (400 mHz, $CDCl_3$): δ 6.86 (s, 1H), 6.65 (s, 1H), 6.32-6.28 (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).

Example 172.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[1-methyl-5-(3-methyl-thiophen-2-yl)-^1H-pyrrol-2-yl]- imidazo[*1,2-b*]pyridazine.



A. 3-(5-Bromo-1-methyl-^1H-pyrrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

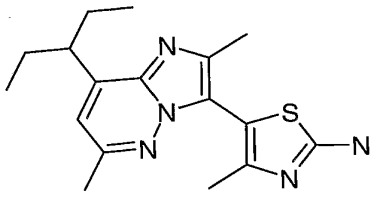
A THF solution (10 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-^1H-pyrrol-2-yl)-imidazo[*1,2-b*]pyridazine (414 mg, 1.40 mmol) is cooled to 0 °C and treated with a THF solution of NBS (250 mg, 1.40 mmol). Within 5 min, the reaction mixture is treated with sat Na_2SO_3 (1 mL) then concentrated. The resulting residue is diluted with ethyl acetate (50 mL) and ished with 50% aq sat'd Na_2SO_3 (2x50 mL). The organic extract is dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (374 mg, 71% yield) as a solid. ES-MS (m/z): calc'd for $C_{18}H_{23}BrN_4$: 374.11; found 375 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): 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).

B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[1-methyl-5-(3-methyl-thiophen-2-yl)-^1H-pyrrol-2-yl]- imidazo[*1,2-b*]pyridazine.

A THF slurry (5 mL) of 3-(5-bromo-1-methyl-^1H-pyrrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (143 mg, 0.38 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 19 mg, 0.023 mmol) is treated with 3-methyl-2-thienyl zinc bromide (Aldrich, 0.5 M in THF, 3.8 mL, 1.9 mmol) then heated to 60 °C for 1 hr. The resulting mixture is poured into sat'd NH_4Cl (25 mL) and extracted with diethyl ether (35 mL). The organic extract is washed with aq. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using 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 hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the product. Only the fractions containing pure desired product, as judged by MS analysis, are collected and give the title compound (82.6 mg, 55% yield) as an oil. ES-MS (m/z): calc'd for $C_{23}H_{28}N_4S$: 392.20; found 393.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): 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).

Example 173.

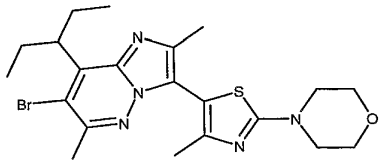
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-ylamine.



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) oxide are added to 3 ml of 2 M NH3 in MeOH and vial is capped with a Teflon® lined cap, heated at 130°C for overnight. The reaction mixture is concentrated under N2 gas and applied onto a silica-gel chromatography column (Hexane: AcOEt: 2 M NH3 in MeOH = 20:20:1) to give 22 mg of the title compound. Yield 54%: mass spectrum (m/e): 330(M+1); ^{1}H-NMR(CDCl3): 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=7.4Hz).

Example 174.

Preparation 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.



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 of NBS (1.92 mmol) are dissolved in 20 ml of CHCl3 and stirred at room temperature overnight. The reaction mixture is washed with sat. $Na_2S_2O_3$, sat. NaCl, dried over Na_2SO_4 and evaporated. The crude materials are

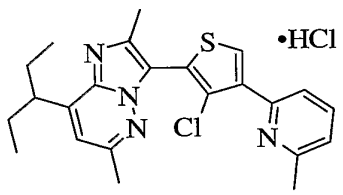
applied onto a silica-gel chromatography column (Hexane:AcOEt=8:1) to give 218 mg of the title compound. Yield 27%. mass spectrum (m/e): 473(M+1); ^{1}H-NMR(CDCl3): 3.44(m, 1H), 2.70(s, 3H), 2.45 (s, 3H), 2.37(s, 3H), 2.03(m, 4H), 0.90(m, 6H).

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 of 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 of morpholine (0.76 mmol) and 97 mg of cesium carbonate (0.3 mmol) are put in 4 ml vial with 3 ml of dry THF. The vial is capped with a Teflon® lined cap and heated at 100°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt = 3:1) to give 30 mg of the title compound. Yield 42%.: mass spectrum (m/e): 479(M+1); ^{1}H-NMR(CDCl3): 3.87(t, 4H, J=5.0Hz), 3.55(t, 4H, J=5.0Hz), 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=7.3Hz).

Example 175.

Preparation of 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.

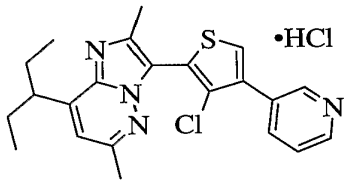


Reike® Zn (0.5 g/ mL solution in THF (1.9 mL,, 1.45 mmol) is added to a flask containing 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.73 mmol). The slurry is heated at 65 °C for 1 hour, placed in a centrifuge for 5 minutes, and the resulting solution is transferred to a flask containing 2-bromo-6-methyl-pyridine (0.12 g, 0.73 mmol) and $PdCl_2$(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 sat. solution of 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 hexanes and ethyl acetate gradient. The resulting product is dissolved in

dichloromethane (5 mL), treated with a 1 M solution of HCl in EtOH (0.35 mL, 0.35 mmol) and concentrated. The residue is recrystallized from ethyl acetate and hexanes furnish the title compound (0.033 g, 0.072 mmol, 11%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.3 Hz, 6H), 1.73-2.02 (m, 4H), 2.68 (s, 3H), 2.81 (s, 3H), 3.21 (s, 3H), 3.88-3.98 (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. for $C_{23}H_{26}Cl_2N_4S$ $(M+H)^+$: 424.2; found: 424.2.

Example 176.

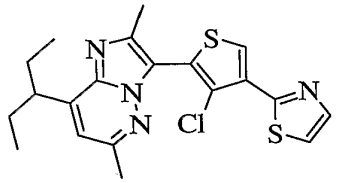
Preparation of 3-(3-chloro-4-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.



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 (0.40 g, 0.97 mmol), Reike® Zn (0.5 g/ mL solution in THF, 2.5 mL, 1.94 mmol), 3-iodo-pyridine (0.30 g, 1.45 mmol), $PdCl_2$(dppf) (0.035 g, 0.048 mmol), and a 1 M solution of HCl in EtOH (0.61 mL, 0.61 mmol) furnish the title compound (0.076 g, 0.17 mmol, 18%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.0 Hz, 6H), 1.71-1.88 (m, 2H), 1.88-2.01 (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), 8.23 (bs, 1H), 8.70 (bs, 1H), 8.89 (bs, 1H), 9.18 (bs, 1H). LC/MS (m/z): calcd. for $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; found: 411.2.

Example 177.

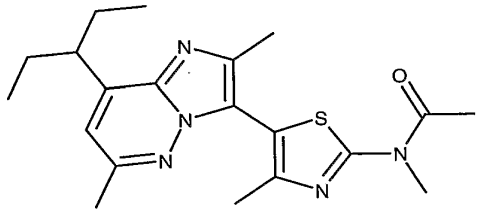
Preparation of 3-(3-chloro-4-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



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® Zn (0.5 g/ mL solution in THF, 1.6 mL, 1.21 mmol), 2-bromo-thiazole (0.11 mL, 1.21 mmol), and $PdCl_2$(dppf) (0.022 g, 0.030 mmol) furnish the title compound (0.012 g, 0.29 mmol, 6.8%). ^{1}H-NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.52 (s, 6H), 3.27-3.43 (m, 1H), 6.73 (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. for $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; found: 417.2.

Example 178.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methyl-acetamide.

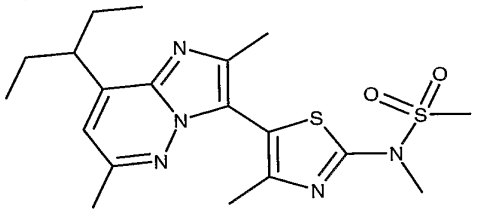


60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 ml of CH_2Cl_2 and 16 mg of acetylchloride (0.2 mmol) is added. The vial is capped with a Teflon® lined cap and shaken at room temperature for 2h. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt = 3:1 and Hexane :AcOEt=2:1) to give 33.8 mg of the title compound. Yield 50%: mass spectrum (m/e): 386(M+1); ^{1}H-NMR(CDCl3): 7.03(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=7.4Hz).

Example 179.

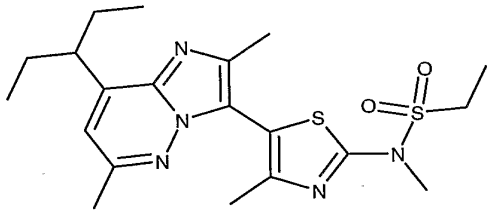
Preparation of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methanesulfonyl-methylamine.



60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 ml of CH2Cl2 and 23 mg of methanesulfonyl chloride (0.2 mmol) is added. The vial is capped with a Teflon® lined cap and shaken at room temperature for 2h. The reaction mixture is concentrated and applied to silica-gel chromatography (Hexane :AcOEt = 2:1) to give 53.8 mg of the title compound. Yield 75%. mass spectrum (m/e): 422(M+1); ^{1}H NMR(CDCl3): 6.96(s, 1H), 3.60(s, 3H), 3.34(m, 1H), 3.19(s, 3H), 2.56(s, 3H), 2.48(s, 3H), 2.29(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.4Hz).

Example 180.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-ethanesulfonyl-methylamine.

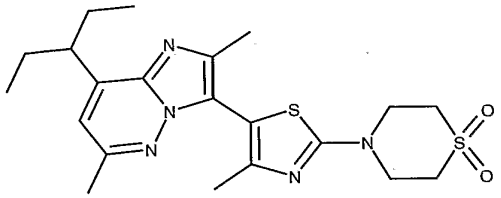


The title compound is prepared by a procedure analogous to Example 178. employing 50 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.15 mmol), 51 mg of triethylamine (0.5 mmol) and 39 mg of ethanesulfonylchloride (0.3 mmol). 48.9 mg, Yield 75%: mass spectrum

(m/e): 436(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.62(s, 3H), 3.42(q, 2H, J=7.4Hz), 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=7.4Hz), 0.90(t, 6H, J=7.5Hz).

Example 181.

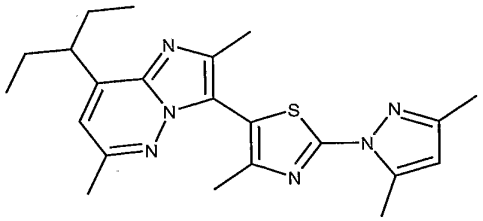
Preparation of 3-[2-(1,1-dioxo-thiomorpholin-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



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 CH_2Cl_2 and 62 mg of mCPBA (0.36 mmol) is added. The reaction mixture is stirred at room temperature for 30 min. The reaction mixture is diluted with CH_2Cl_2, washed with sat. NaHCO3 and sat. NaCl. The separated organic layer is dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt:2 M NH3 in MeOH=10:3:1) to give 20.3 mg of the title compound. Yield 33%: mass spectrum (m/e): 448(M+1). ^{1}H-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.

Preparation of 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.

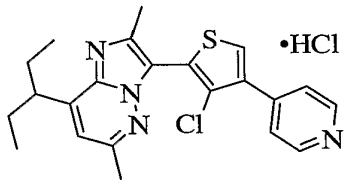
The title compound is prepared essentially as described in Example 135 using hydrazine. MS found (M+1) 345.

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 of {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 of 2,4-pentanedione (0.8 mmol) are dissolved in 1.0 ml of AcOH and heated at 100°C for 2 h. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane : AcOEt = 5:1) to give 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.

Preparation of 3-(3-chloro-4-pyridin-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.

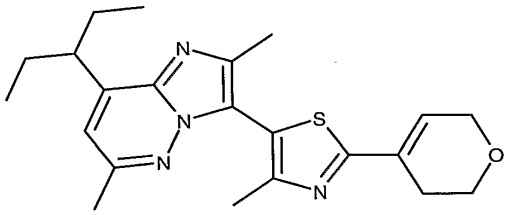


A solution of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), 4-pyridyl-boronic acid (0.82, 0.67 mmol), a 2 M solution of Na_2CO_3 (0.5 mL, 0.91 mmol), and *n*-PrOH (2.5 mL) are degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (0.0027 g, 0.012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added, and the solution heated at a 90 °C overnight. The solution is diluted with ethyl acetate (40 mL) and washed with a 10 % solution of Na_2CO_3 (30 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO flash chromatography (20%-30% EtOAc gradient). The resulting product is dissolved in dichloromethane (5 mL), treated with a 1 M solution of HCl in

EtOH (0.35 mL, 0.35 mmol), and concentrated. The residue is recrystallized from acetonitrile and ethyl acetate furnish the title compound (0.15 g, 0.34 mmol, 56%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (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. for $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; found: 411.2.

Example 184.

Preparation of 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 of 3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.93 mmol) is dissolved in 10 ml of dry THF and cooled to –78°C. 0.6 ml of n-BuLi 2.0 M in hexane (1.2 mmol) is added and stirred at –78°C for 30 min. 141 mg of tetrahydro-*4H*-pyran-4-one (1.41 mmol) is added and stirred at –78°C for 2 h. The reaction mixture is diluted with AcOEt, washed with sat. NH4Cl , dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt : 2 M NH3 in MeOH =10:3:1) to give 152 mg of the title compound. Yield 40%.: mass spectrum (m/e): 415(M+1). ^{1}H NMR ($CDCl_3$): δ 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, OH), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 1.88 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).

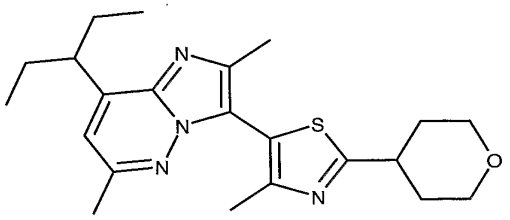
B. 3-[2-(3,6-Dihydro-*2H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

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) is dissolved in 5 ml of CH2Cl2

and 112 mg of triethylsilane (0.96 mmol) and 717 mg of trifluoroacetic acid (6.3 mmol) are added. The reaction mixture is stirred at room temperature for 1h. The reaction mixture is stirred under reflux for 1 h and cooled down to room temperature. The solvent is removed in *vacuo*. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt: 2 M NH3 in MeOH =10:3:1) to give 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), 3.98 (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.

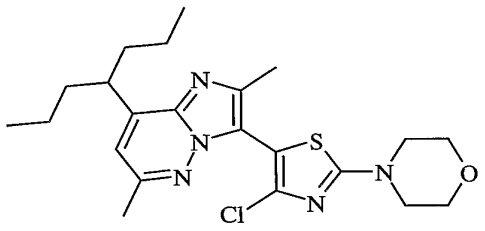
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(tetrahydro-pyran-4-yl)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.



Add 3-[2-(3,6-dihydro-2*H*-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 absolute ethanol (50 ml) to a pressure vessel. Purge the reaction vessel with nitrogen, purge the reaction vessel with hydrogen, pressurize the reaction mixture with hydrogen (415 KPa), seal the vessel, agitate the reaction and heat to 40 °C. Continue the reaction for 18 hours then turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the 5% palladium on carbon. The filtrate is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt : 2 M NH_3 in MeOH = 10:3:1) to give 12.8 mg of the title compound. Yield 23%. mass spectrum (m/e): 399(M+1). ^{1}H NMR ($CDCl_3$): δ 6.73 (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.



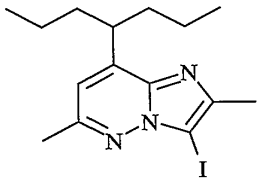
A. 6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine.

6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine can be made using chemistry described in J. Heterocylic Chem. **1991**, *28*, 583. A 250 mL three neck round bottom flask is charged with 3-amino-6-methyl pyridazine (2.5 g, 0.229 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 equiv), silver nitrate (3.87 g, 0.0229 moles, 1.0 equiv), and valproic acid (7.21 g, 7.95 mL, 0.050 moles, 2.2 equiv) are added to the reaction mixture. The reaction is heated to 75 °C. As the reaction mixture is heating, a solution of $(NH_4)_2S_2O_8$ (7.85 g, 0.0344 moles, 1.5 equiv) in 40 mL of water is slowly added via an addition funnel over a period of 30 minutes. The reaction mixture is heated at 70-80 °C for two more hours. The reaction mixture is cooled and dichoromethane is added. The reaction is made basic with a 30% aqueous NaOH solution and filtered through a short Celite® plug. The organic layer is separated, and the aqueous layer is extracted two more times with dichoromethane. The combined organic extracts are dried over Na_2SO_4. The solvent is evaporated and the crude material is purified using silica gel chromatography with a 2.0 N solution of NH_3 in MeOH and methylene chloride 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 is charged with 6-methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine (0.611 g, 0.00295 moles, 1 equiv), ethanol 2B (30 mL), and chloroacetone (0.382 g, 0.328 ml, 0.00412 moles, 1.4 equiv). The reaction mixture is heated at 75 °C overnight and then cooled to room temp. $NaHCO_3$ (0.371 g, 0.00442 moles, 1.5 equiv) is slowly added to the reaction mixture that is then heated to 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 is evaporated to obtain a brown oil which is purified via silica gel chromatography. The material is eluted with a hexanes and ethyl acetate gradient to obtain 0.511 g of the final products. Two peaks are identified in the lc/ms. The mixture is used "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.



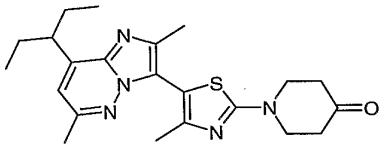
A 50 mL round bottom flask is charged with 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-*b*]pyridazine (0.51 g, 0.0021 moles) and acetonitrile (3 mL). The reaction mixture is placed on an ice bath and NIS (0.468 g, 0.00208 moles) is added neat. The reaction is stirred overnight and the ice bath melts. The next day, the reaction mixture is partitioned between dichloromethane and a saturated aqueous solution of $NaHCO_3$. The organic layer is collected and the aqueous layer is extracted two more times with dichloromethane. The organic extracts are combined, washed with brine, and dried over Na_2SO_4. The solvent is evaporated and the crude material is purified via silica gel chromatography eluting with hexanes and then 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 is charged with 3-iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-*b*]pyridazine (0.200 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 equiv), $Pd(dba)_2$ (0.0092 g, 0.0000161 moles, 0.03 equiv), PPh_3 (0.00847 gram, 0.000323 moles, 0.060 equiv) and DMF (2.0 mL). Nitrogen is bubbled through the reaction mixture for 15 minutes; then, the reaction mixture is heated at 130 °C overnight. The next day, the reaction mixture is partitioned between Et_2O and a saturated solution of NH_4Cl. The aqueous layer is extracted twice more with Et_2O. The organic extracts are combined, washed 2-3 times with H_2O, washed once with brine, and dried over Na_2SO_4. The solvents are evaporated in vacuo and the crude reaction mixture is purified via silica gel chromatography. Yield = 0.1737 g (72%). ^{1}H-NMR ($CDCl_3$), δ 0.87 (t, *J* = 7 Hz, 6H), 1.14- 1.37 (m, 4H), 1.74 (q, *J* = 8 Hz, 4H), 2.54 (s, 3H), 2.50 (s, 3H), 3.48 (m, 1H), 3.53 (t, *J* = 5 Hz, 4H), 3.83 (t, *J* = 5 Hz, 4H), 6.71(br s, 1H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{30}ClN_5OS$ $(M+H)^+$: 448; found: 448.

Example 187.

Preparation of 1-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidin-4-one.



A. 8-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,4-dioxa-8-aza-spiro[4.5]decane.

100 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 mmol), 182 mg of 4-piperidineethylene ketal (1.27 mmol) and 244 mg of Cs2CO3 (0.75 mmol) are put into 4.0 ml vial with 2.0 ml of THF. The vial is capped with a Teflon® lined cap 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 give 116 mg of the title compound. Yield 100%. mass spectrum

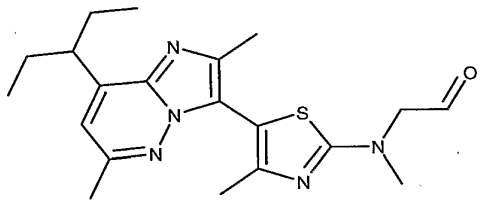
(m/e): 456(M+1). ^{1}H NMR ($CDCl_3$): δ 6.69 (s, 1H), 4.05 (s, 4H), 3.70 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.90-1.78 (m, 8H), 0.90 (t, J = 7.2 Hz, 6H).

B. 1-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidin-4-one.

70 mg of 8-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,4-dioxa-8-aza-spiro[4.5]decane (0.15 mmol) is dissolved in 10.ml of conc. HCl and stirred at room temperature for 2 h. The reaction mixture is neutralized with sat. NaHCO3, extracted with CH2Cl2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=2:1) to give 33.2 mg of the title compound . Yield 52%. mass spectrum (m/e): 412(M+1). ^{1}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.

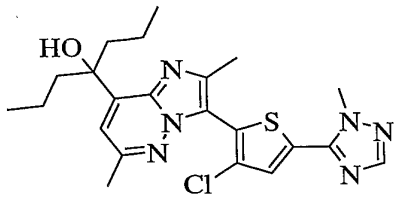
Preparation of ({5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methyl-amino)-acetaldehyde.



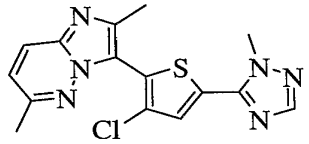
85 mg of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- N-{[1,3]dioxolan-2-ylmethyl-methylamine (0.2 mmol) is dissolved in 2 ml of conc. HCl and stirred at 50°C for 30 min. The mixture is cooled to room temperature and neutralized with sat. NaHCO3. The mixture is extracted with CH2Cl2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (CH2Cl2:MeOH=20:1) to give 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.

Preparation of 4-{3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-heptan-4-ol.

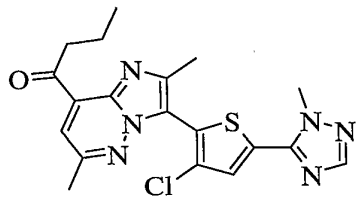


A. 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.32 g, 2.17 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-*1H*-[1,2,4]triazole (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) and DMF (6 mL) is de-gassed for 15 minutes with N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) and PPh_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 sat. NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) furnish the title compound (0.29 g, 0.84 mmol, 39%). ^1H 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. for $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; found: 345.2.

B. 1-{3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-butan-1-one.



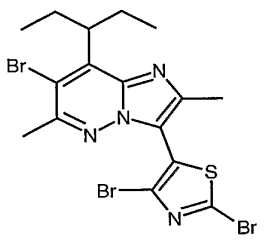
A solution of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.58 mmol), *N*-methoxy-*N*-methyl-butylamide (Wolberg, M. et. al. *Chem. Europ. J.* 2001, 7, 4562.) (0.084 g, 0.64 mmol) in THF (3 mL) is cooled to a -78 °C, and a 2.0 M solution of LDA in heptane/ THF/ ethyl benzene (0.58 mL, 1.16 mmol) is added. The solution is warmed to ambient temperature, diluted with dichloromethane (20 mL), and washed with a sat. 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 furnish the title compound (0.11 g, 0.27 mmol, 46%). ^{1}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): calcd. for $C_{19}H_{19}ClN_6OS$ $(M+H)^+$: 415.1; found: 415.3.

C. 4-{3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-heptan-4-ol.

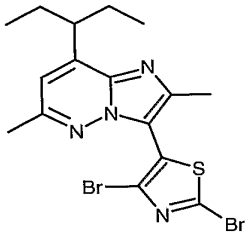
A solution of 1-{3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-butan-1-one (0.15 g, 0.36 mmol) and THF (5 mL) is cooled to 0°C, and a 2.0 M propyl magnesium bromide solution in diethylether (0.22 mL, 0.43 mmol) is added. The reaction is warmed to ambient temperature, diluted with ethyl acetate (30 mL), and washed with a sat. 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 furnish the title compound (0.016 g, 0.017 mmol, 47%). ^{1}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), 6.11 (bs, 1H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{27}ClN_6OS$ $(M+H)^+$: 459.2; found: 459.3.

Example 190, 191, and 192.

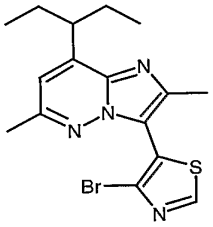
Preparation of 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



190.



191.



192.

A. 8-(1-ethyl-propyl)-2,6-dimethyl-3-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 of thiazole (35.2 mmol), 378 mg of triphenylphosphine (1.44 mmol) and 4.71 g of Cs2CO3 (14.5 mmol) are combined with 25 ml of DMF and N2 gas is bubbled in for 30 min. 330 mg of Pd2dba3 (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 CH2Cl2, and the CH2Cl2 layer is separated, washed with sat. NaCl and dried over Na2SO4. The solvents are removed *in vauo* and crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt = 3:1) to give 1.48 g of the title compound. Yield 70%. mass spectrum (m/e): 301(M+1); ^{1}H-NMR(CDCl3): 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=7.5Hz).

B. 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; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

1.05 g (3.5 mmol) of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine and 1.56 g of NBS (8.75 mmol) are dissolved in 50 ml of CH2Cl2 and stirred at room temperature for 3 days. The reaction mixture is diluted with CH2Cl2 and washed with sat. $Na_2S_2O_3$ and sat. NaCl. The separated organic layer is dried over Na_2SO_4 and evaporated. The reaction mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 20:1→8:1) to give three 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%); and

77 mg of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (6%).

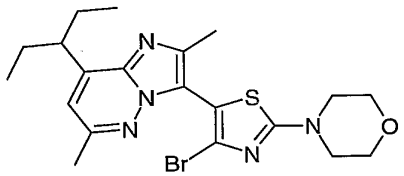
7-Bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 538(M+1); ^{1}H-NMR(CDCl3): 3.45(m, 1H), 2.71(s, 3H), 2.52(s, 3H), 2.38(m, 2H), 2.02(m, 2H), 0.88(t, 6H, J=7.5Hz);

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}H-NMR(CDCl3): 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=7.5Hz); and

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}H-NMR(CDCl3): 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=7.5Hz).

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 of morpholine (1.1 mmol) and 215 mg of Cs2CO3(0.66 mmol) are put in a 4 ml vial with dry THF, and the vial is

capped with a Teflon cap. The vial is heated at 120°C for overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane :AcOEt :2 M NH3 in MeOH = 9:3:1) to give 72.7 mg of the title compound. Yield 71%. mass spectrum (m/e): 465(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.87(t, 4H, J=5.1Hz), 3.58(t, 4H, J=5.1Hz), 3.35(m, 1H), 2.57(s, 3H), 2.53(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.5Hz).

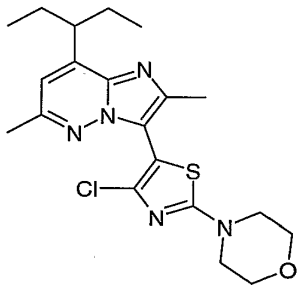
The following compounds are prepared essentially as described in Example 193. Examples 194-197 use 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol) and the named amine. Example 198. uses 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and the named amine:

Ex	Name	Amine	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
194	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-methyl-amine	Methyl-amine	6.75 (s, 1H), 5.85 (s, NH), 3.37 (m, 1H), 3.07 (d, J = 5.3 Hz, 3H), 2.59 (s, 3H), 2.55 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	409
195	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	Dimethyl-amine	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J=7.3Hz)	423
196	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	N-2-methoxy-ethyl-methyl-amine	6.71 (s, 1H), 3.76 (m, 2H), 3.71 (m, 2H), 3.42 (s, 3H), 3.35 (s, 1H), 3.21 (s, 3H), 2.57(s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	467

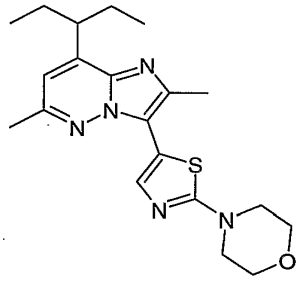
197	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	N-methyl-i-propyl-amine	6.72 (s, 1H), 4.43 (m, 1H), 3.36 (m, 1H), 3.0 (s, 3H), 2.57 (s, 3H), 2.54 (s, 3H), 1.86 (m, 4H), 1.31 (s, 3H), 1.29 (s, 3H), 0.90 (t, J = 7.4 Hz, 6H).	451
198	N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-bromo-thiazol-2-yl}-morpholine	Morpholine	3.87 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 7.8 Hz, 4H), 3.43 (m, 1H), 2.71(s, 3H), 2.50 (s, 3H), 2.38 (m, 2H), 2.01 (m, 2H), 0.88 (t, J = 7.5 Hz, 6H).	544

Example 199 and 200.

Preparation of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine and N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine.



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 put in a 4 ml vial with 2 ml of dry DMF and capped with a Teflon cap. The vial is heated at 120°C overnight. The reaction mixture is filtered, washed with CH2Cl2 and the filtrate is concentrated. The crude product mixture is 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%), and

7.2 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (22%).

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}H-NMR(CDCl3): 6.73(s, 1H), 3.88(t, 4H, J=5.0 Hz), 3.57(t, 4H, J=5.0Hz), 3.35(m, 1H), 2.57(s, 3H), 2.52(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.5Hz.

N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine mass spectrum (m/e): 386(M+1); ^{1}H-NMR(CDCl3): 7.75(s, 1H), 6.70(s, 1H), 3.91(t, 4H, J=5.0Hz), 3.61(t, 4H, J=5.0Hz), 3.34(m, 1H), 2.67(s, 3H), 2.61(s, 3H), 1.85(m, 4H), 0.88(t, 6H, J=7.5Hz).

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 20L reactor flask under nitrogen is charged with 2900 ml of dry and degassed DMF then with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[1,2-b]pyridazine (287 g, 0.836 mol), 2-morpholino-4-chlorothiazole (205.4 g, 1.01 mol, 1.2 equv.), $Pd(OAc)_2$ (3.74 g, 7.91 mmol, 0.01 equiv.), triphenylphosphine (8.77g, 33.1 mmol, 0.04 equiv.), Copper iodide (8 g, 41.59 mmol, 0.05 equiv.) and cesium carbonate (544.9 g, 1.65 mol). The reaction mixture is heated at 120°C. After 16 h at 120°C, 1.87 g of $Pd(OAc)_2$ and 4.38 g of triphenylphosphine more is added. After 1 h, the mixture is cooled, quenched with NH_4Cl solution (4300 mL) and extracted with MTBE (2900 mL), the aqueous phase is extracted twice more with 2000 ml of MTBE. The organic phases are washed with sat NaCl aq (2000 mL), then treated with charcoal 72 g in flask bottle and filtered on Celite®. The filtrate is concentrated under vacuum to afford 373.8 g (79.3%) of the title compound which is 81.4%-area HPLC analysis the rest being solvent and with no detectable Example 200 by-product.

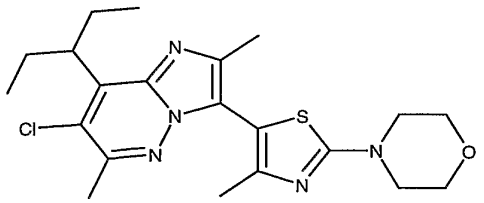
The following title compounds are prepared essentially as described in Examples 199 and 200 Method A:

Example #	Name	Starting material	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
201	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.51 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).	378
202	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	7.74 (s, 1H), 6.67 (s, 1H), 3.35 (m, 1H), 2.23 (s, 6H), 2.67(s, 3H), 2.61 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	344
203	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	6.71 (s, 1H), 3.76 (t, J = 5.3 Hz, 2H), 3.71 (t, J = 5.1 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 3.20 (s, 3H), 2.58 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	423
204	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-	7.72 (s, 1H), 6.68 (s, 1H), 3.80 (t, J = 5.7 Hz, 2H), 3.72 (t, J = 5.7 Hz, 2H), 3.42 (s, 3H), 3.35 (m, 1H), 3.26 (s, 3H), 2.67 (s, 3H), 2.61 (s, 3H), 1.84	388

	methylamine	methylamine	(m, 4H), 0.88 (t, J = 7.7 Hz, 6H).	
205	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	6.71 (s, 1H), 4.48 (m, J = 7.4, 13.2 Hz, 1H), 3.34 (m, J = 7.6, 14.4 Hz, 1H), 3.04 (s, 3H), 2.76 (s, 3H), 2.61 (s, 3H), 1.85 (m, 4H), 1.31 (d, J = 7.1 Hz, 6H), 0.88 (t, J = 7.3 Hz, 6H).	407
206	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-isopropyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	7.72 (s, 1H), 6.67 (s, 1H), 4.48 (m, 1H), 3.33 (m, 1H), 3.03 (s, 3H), 2.66 (s, 3H), 2.60 (s, 3H), 1.84 (m, 4H), 1.31 (d, J = 6.8, 6H), 0.88 (t, J = 7.2 Hz, 6H).	371

Example 207.

Preparation of N-{5-[7-chloro-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.

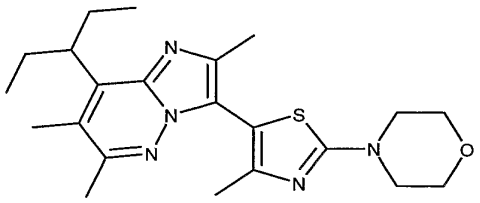


50 mg of N-{5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine (0.1 mmol) is dissolved in 2.0 ml of

dry DMF and 31 mg of CuCl (0.3 mmol) is added. The vial is capped with a Teflon® lined cap and heated at 120°C for overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 39.2 mg of the title compound. Yield 87%. mass spectrum (m/e): 435(M+1). 3.88 (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.

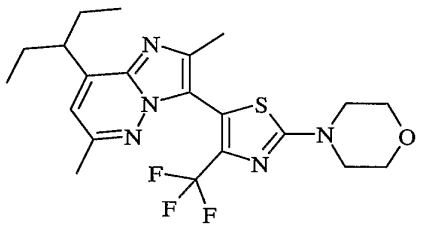
Preparation of N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6,7-trimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.



50 mg 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 4 ml of Et2O and cooled to –78°C. 0.09 ml of n-BuLi 1.6M in hexane (0.15 mmol) is added at –78°C and stirred at –78°C for 20 min. 43 mg of iodomethane (0.3 mmol) is added to the mixture and stirred at –78°C and allowed to come to room temperature overnight. The reaction is quenched with sat. NH4Cl and extracted with Et2O. 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 give 29.6 mg of the title compound. Yield 69%. mass spectrum (m/e): 414(M+1). ^{1}H NMR ($CDCl_3$): 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.

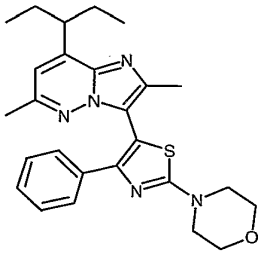
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-trifluoromethyl-thiazol-2-yl}-morpholine.



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 of sodium trifluoroacetate (0.74 mmol) are dissolved in 3 ml of DMF/toluene = 2/1. N2 gas is bubbled into the mixture for 20 min and 141 mg of CuI (0.74 mmol) is added. The vial is sealed and heated in the microwave at 210°C for 30 min. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1 and CH3CN : CH2Cl2 : Hexane = 5 : 45 : 50) to give 64.3 mg of the title compound. Yield 38%. mass spectrum (m/e): 454(M+1). ^{1}H NMR ($CDCl_3$): 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.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-phenyl-thiazol-2-yl}-morpholine.

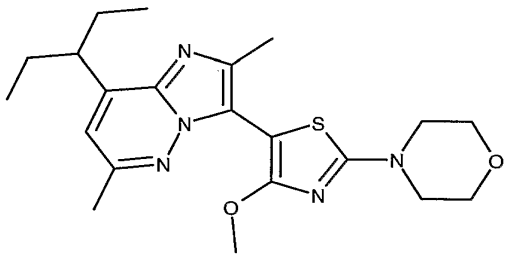


50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), 40 mg of phenylboronic acid (0.33 mmol) and 0.27 ml of 2 M Na2CO3aq.(0.55 mmol) are put in 2.5 ml of DME / water / EtOH = 7 / 3 / 1. N2 gas is bubbled in the mixture for 20 min and 20 mg of Pd(PPh3)4

(0.017 mmol) is added. The vial is sealed and heated at 160°C for 30 min in Microwave. The reaction mixture are added CH2Cl2 and water and 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 give 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.

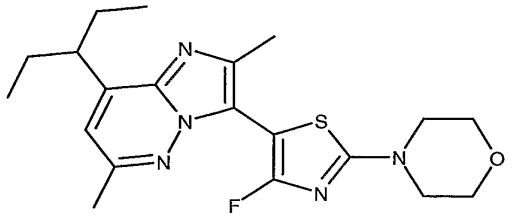
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methoxy-thiazol-2-yl}-morpholine.



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 of sodium methoxide (0.44 mmol) and 21 mg of CuI (0.11 mmol) are put into 4 ml vial with MeOH 3 ml 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 give 32.8 mg of the title compound. Yield 36%. Mass spectrum (m/e): 416(M+1). ^{1}H NMR ($CDCl_3$): 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.

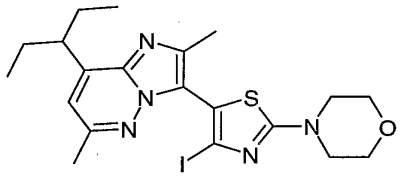
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-fluoro-thiazol-2-yl}-morpholine.



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) is dissolved in 4 ml of diethylether and cooled to –78°C and 0.1 ml of n-BuLi 1.6M in hexane (0.16 mmol) is added at –78°C and stirred at –78°C for 20 min. 104 mg of N-fluorobenzene sulfonimide (0.33 mmol) in 2 ml of toluene is added at –78°C and stirred at room temperature for 1h. sat. NH4Cl is added, and the mixture is extracted with Et2O, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 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), 2.58 (s, 3H), 2.54 (s, 3H), 1.84 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 213.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-iodo-thiazol-2-yl}-morpholine.

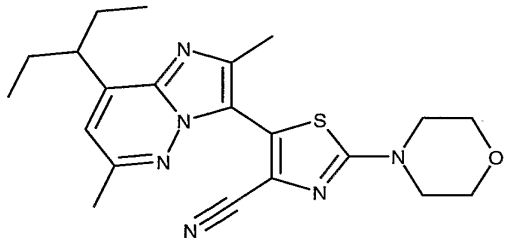


50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), 30 mg of CF_3CO_2Na (0.22 mmol) and 42 mg of CuI (0.22 mmol) are put into 4 ml vial with DMF / toluene = 2:1. The vial is capped with a Teflon cap and heated at 150°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane :AcOEt = 5 : 1) to give 54 mg of the

title compound. 96%. Mass spectrum (m/e): 512 (M+1). ^{1}H NMR ($CDCl_3$): 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.

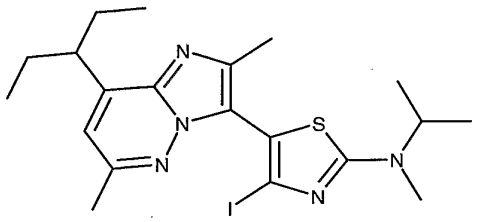
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-2-morpholin-4-yl-thiazole-4-carbonitrile



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 of CuCN (0.33 mmol) are put into 4 ml vial with 2 ml of DMF and the vial is capped 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 give 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.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-iodo-thiazol-2-yl}-N-isopropyl-methylamine.

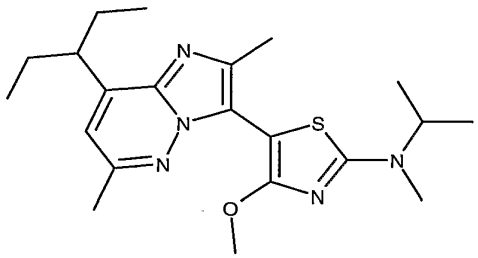


The title compound is prepared essentially as described in Example 213, employing N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-

bromo-thiazol-2-yl}-N-isopropyl-methylamine to give 17.9 mg. Yield 22%: mass spectrum (m/e):498 (M+1). ^{1}H NMR ($CDCl_3$): 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.

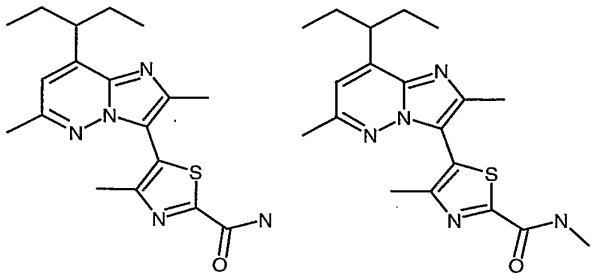
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methoxy-thiazol-2-yl}-N-isopropyl-methylamine.



The title compound is prepared essentially as described in Example 211, employing N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-bromo-thiazol-2-yl}-N-isopropyl-methylamine to give 52.7. Yield 36%: mass spectrum (m/e):402(M+1). ^{1}H NMR ($CDCl_3$): 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), 1.29 (d, J = 6.7 Hz, 6H), 0.88 (t, J = 8 Hz, 6H).

Example 217 and 218.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide and 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid N-methylamide.



217. 218.

180 mg of 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 are put into 4 ml vial with 2 ml of dry DMF. The vial is closed with a Teflon can and heated at 130°C overnight. The crude reaction mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 1:1 →1:3) to give

52.1 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide (32%) and

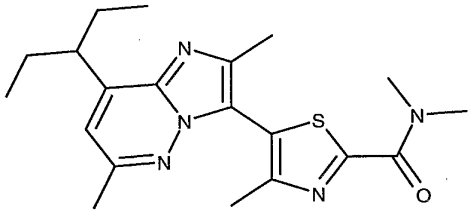
7.6 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid methylamide.

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide: mass spectrum (m/e): 358(M+1) ^{1}H NMR ($CDCl_3$): δ 7.21 (s, NH), 6.76 (s, 1H), 5.59 (s, NH), 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-thiazole-2-carboxylic acid methylamide: mass spectrum (m/e): 372(M+1). ^{1}H NMR ($CDCl_3$): 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-thiazole-2-carboxylic acid dimethylamide.

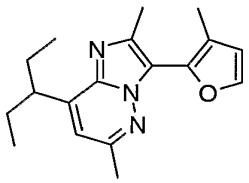


5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide (46 mg, 0.13 mmol) and 28 mg of sodium *tert*-Butoxide (0.30 mmol) are put into 4 ml of dry DMSO and stirred at room temperature for 5 min. 141 mg of iodomethane (1.0 mmol) is added and stirred at room temperature for 1 h.

Water is added, and the mixture is extracted with CH_2Cl_2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=3:1) to give 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.

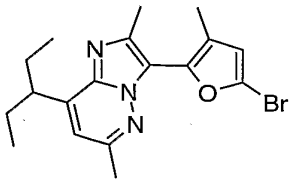
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo[*1,2-b*]pyridazine.



A THF solution (5 mL) of 3-methylfuran (Acros, 232 mg, 2.83 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol). After addition of the nBuLi, the solution is warmed to 0 °C for 15 minutes, then to room temperature for an additional 5 minutes. The reaction mixture is then cooled to -78 °C and treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 5.8 mL, 2.9 mmol). The resulting mixture is warmed to room temperature and treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (400 mg, 1.17 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 95 mg, 0.12 mmol). The mixture is heated to 60 °C for 4 hours, then poured into 1 N HCl (60 mL) and extracted with ethyl acetate (2x60 mL). The combined organic extracts are washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound as an oil pyridazine (149 mg, 43% yield). ES-MS (m/z): calc'd for $C_{18}H_{23}N_3O$: 297.2; found 298.5 (M+H); ^{1}H NMR (400 mHz, $CDCl_3$): 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.

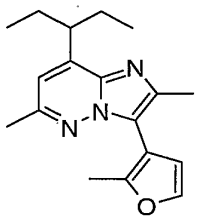
Preparation of 3-(5-bromo-3-methyl-furan-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A CH_2Cl_2 solution (4 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo[*1,2-b*]pyridazine (32.4 mg, 0.11 mmol) is cooled to 0 °C under a $CaSO_4$ 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 H_2O (25 mL) and extracted into CH_2Cl_2 (2x25 mL). The combined organic extracts are washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 10% ethyl acetate in hexane) to elute the title compound (26.3 mg, 64% yield) as a solid. ES-MS (m/z): calc'd for $C_{18}H_{22}BrN_3O$: 375.1; found 376.2 (M+H); ^1H NMR (400 mHz, $CDCl_3$): 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), 1.93-1.77 (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. 3-Bromo-2-methyl furan.

A THF solution (10 mL) of 2,3-dibromofuran (Lancaster, 5.54 gm, 24.5 mmol) under N_2 is treated with $PdCl_2(PPh_3)_2$ (860 mg, 1.2 mmol) and stirred for 10 minutes at

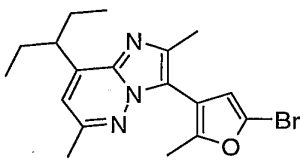
room temperature. The solution is then treated with CH_3ZnCl (Aldrich, 2.0 M in THF, 15 mL, 30 mmol). The resulting mixture is stirred at room temperature overnight then poured into 1 N HCl and extracted into diethyl ether. The organic extract is washed with sat. NaCl, dried over Na_2SO_4, and filtered. The filtrate is then distilled and the product is collected at 120-125 °C to give the title compound as a colorless oil (1.71 gm, 43% yield). ^1H NMR (400 mHz, $CDCl_3$): 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.

A THF solution (10 mL) of 3-bromo-2-methyl furan (prepared as described above) (1.06 gm, 6.58 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 4.1 mL, 6.6 mmol). After 10 minutes at -78 °C, the mixture is treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 13.2 mL, 6.6 mmol). The resulting mixture is warmed to room temperature then treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.13 gm, 3.29 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 257 mg, 0.31 mmol). The mixture is heated to 60 °C for 4 hours, then poured into sat. NH_4Cl (50 mL) and extracted with diethyl ether (2x50 mL). The combined organic extracts are washed with sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title product (685 mg, 70% yield) as an oil. ES-MS (m/z): calc'd for $C_{18}H_{23}N_3O$: 297.2; found 298.2 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 7.45 (d, J = 2.0 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.

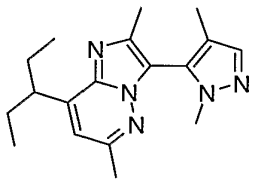
Preparation of 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A CH_2Cl_2 solution (2 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine (42.3 mg, 0.14 mmol) under a $CaSO_4$ drying tube is treated with N-bromosuccinimide (27.6 mg, 0.16 mg). After 30 minutes the reaction mixture is poured into H_2O (25 mL) and extracted into CH_2Cl_2 (2x25 mL). The combined organic extracts are washed with sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the title product (36.9 mg, 70% yield) as a white solid. ES-MS (m/z): calc'd for $C_{18}H_{22}BrN_3O$: 375.1; found 376.3 (M+H); ^{1}H NMR (400 mHz, $CDCl_3$): 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), 1.90-1.73 (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.

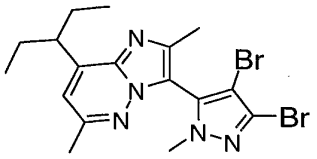


n-BuLi (1.3 ml, 2.09 mmol) is stirred in THF (4 ml), under N_2, and cooled to –72^{0}C. 1,4-dimethyl-*1H*-pyrazole (170 mg, 2.04 mmol, in THF, 1 ml) is added slowly, stirred for 5 min. then allowed to warm to ambient temp. and stirred for 45 min. The mixture is cooled to –72°C and a zinc chloride solution (4.3 ml, 2.14 mmol, 0.5 M in toluene) added, warmed to ambient temp. and treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 40 mg, 0.05 mmol). The mixture is heated to 65^{0}C overnight, cooled to ambient temp., added to water and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 50 % ethyl acetate in hexane) to elute the product. The title compound is obtained (0.7% yield). ES-MS (m/z): calc'd for $C_{18}H_{25}N_5$: 311.4; found 312.2 $(M+H)^+$. ^{1}H 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.

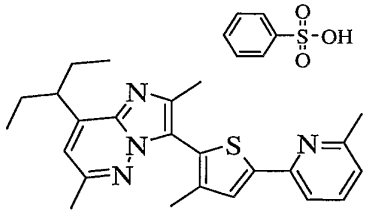
Preparation of 3-(4,5-dibromo-2-methyl-*2H*-pyrazol-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (300 mg, 1.4 mmol), 3,4,5-tribromo-1-methyl-*1H*-pyrazole (700 mg, 2.1 mmol) and cesium carbonate (900 mg, 2.8 mmol) are stirred in DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. $PdCl_2(PPh_3)_2$ (14 mg) is added and the mixture heated to 130°C overnight. The mixture is added to water and extracted twice with EtOAc. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title product (204 mg, 32% yield). ES-MS (m/z): calc'd for $C_{17}H_{21}Br_2N_5$: 455.2; found 455.9 $(M+H)^+$. ^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.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine benzenesulfonic acid.

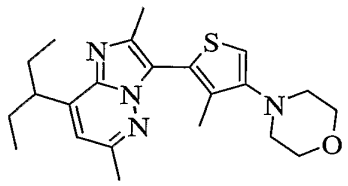


To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.23 g, 0.57 mmol) and MeOH (1

mL) is added a solution of benzenesulfonic acid (0.096 g, 0.57 mmol) and MeOH (1 mL). The solution is concentrated to furnish the title compound (0.32 g, 0.57 mmol, >99%). ^{1}H 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), 2.88 (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. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; found: 405.4.

Example 227.

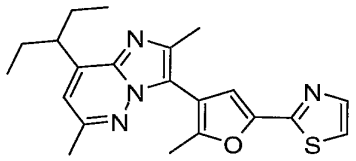
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-morpholin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30g, 0.76 mmol), morpholine (0.10 mL, 1.15 mmol), $Pd_2(dba)_3$ (0.035 g, 0.038 mmol), and 2-dicyclohexylphosphino-biphenyl-2'-(N,N-dimethyl-amino)biphenyl (0.018 g, 0.046 mmol) is added 1 M LiHMDS (1.9 mL, 1.91 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 purified by ISCO (15%-30% EtOAc gradient), dissolved in Et_2O (20 mL) and extracted with 1 M HCl (2 x 30 mL). The aqueous layer is washed with Et_2O (20 mL), made basic with 5 M NaOH (15 mL), extracted with EtOAc (2 x 20 mL), the combined organic layers washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.047 g, 0.12 mmol, 16%). ^{1}H 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. for $C_{22}H_{30}N_4OS$ $(M+H)^+$: 399.2; found: 399.2.

Example 228.

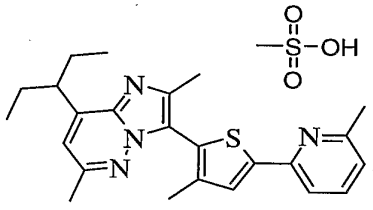
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.



A THF solution (5 mL) of 2-bromothiazole (Aldrich, freshly distilled, 75.0 μL, 0.84 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 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 is warmed to room temperature then treated with a THF slurry (1 mL) containing 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 $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 22 mg, 0.027 mmol). The mixture is heated overnight at 60 °C, then poured into sat'd NH_4Cl and extracted with diethyl ether. The organic extract is washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (45.8 mg, 75% yield) as an oil. ES-MS (m/z): calc'd for $C_{21}H_{24}N_4OS$: 380.17; found 381.1 $(M+H)^+$. ^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), 0.88 (t, J = 7.5 Hz, 6H).

Example 229.

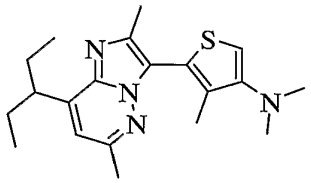
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine; compound with methanesulfonic acid.



To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (0.55 g, 1.36 mmol) and MeOH (6 mL) is added methane sulfonic acid (0.088 mL, 1.36 mmol). After one hour the solution is concentrated and the solution is treated with Darco-60® for 1 hour, filtered and concentrated to furnish the title compound (0.68 g, 1.36 mmol, >99%). ^{1}H NMR ($CDCl_3$: CD_3OD 95:5) 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), 2.90 (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. for $C_{25}H_{32}N_4O_2S_2$ $(M+H)^+$: 405.6; found: 405.6.

Example 230.

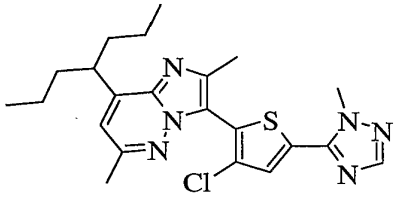
Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-3-yl}-dimethyl-amine.



To a –78 °C solution of dimethyl-(4-methyl-thiophen-3-yl)-amine (0.43 g, 3.06 mmol) and THF (5 mL) is added 1.6 M *n*-BuLi (1.91 mL, 3.06 mmol). The solution is stirred for 1 hour, then 0.5 M $ZnCl_2$ (6.1 mL, 3.06 mmol) is added and the solution warmed to ambient 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 $PdCl_2$(dppf) (0.075 g, 0.10 mmol) is added and the solution heated at 65 °C overnight. The solution is diluted with EtOAc (35 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% -30% EtOAc gradient) furnish the title compound (0.13 g, 0.36 mmol, 18%). ^{1}H 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. for $C_{20}H_{28}N_4S$ $(M+H)^+$: 357.2; found: 357.2

Example 231.

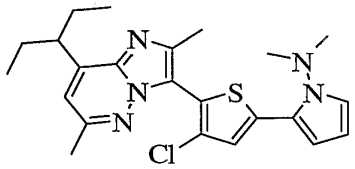
Preparation of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



A slurry of 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine (below) (0.30 g, 1.22 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-[1,2,4]triazole (below) (0.41 g, 1.47 mmol), KOAc (0.60 g, 6.11 mmol), TBABr (0.39 g, 1.22 mmol), and NMP (3 mL) is de-gassed with N_2 for 30 minutes. $Pd(OAc)_2$ (0.014 g, 0.061 mmol) and TDBPP (0.040 g, 0.061 mmol) are added and the solution heated at 125 °C for 2.5 hours. The solution is diluted with EtOAc (50 mL), washed with water (3 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-40% EtOAc gradient) furnish the title compound (0.30 g, 0.68 mmol, 56%). ^1H NMR ($CDCl_3$) 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), 7.48 (s, 1H), 7.90 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}ClN_6S$ $(M+H)^+$: 443.2; found: 443.3.

Example 232.

Preparation of (2-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophen-2-yl}-pyrrol-1-yl)-dimethyl-amine.

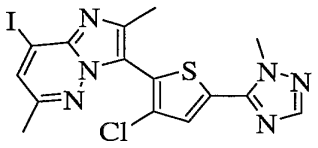


Using a procedure analogous to Example 27, 1-(dimethylamino)-pyrrole (0.20 mL, 1.65 mmol), THF (4 mL), 1.6 M *n*-BuLi (1.10 mL, 1.73 mmol), 0.5 M $ZnCl_2$ (3.46 mL, 1.73 mmol), 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.34 g, 0.82 mmol) and $PdCl_2$(dppf) (0.030 g, 0.041 mmol),

furnish the title compound (0.17 g, 0.38 mmol, 46%). ^{1}H NMR ($CDCl_3$) 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, 3.2 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. for $C_{23}H_{28}ClN_5S$ $(M+H)^+$: 442.2; found: 442.3.

Example 233.

Preparation of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-Chloro-thiophene-2-carbonitrile.

A 22-L reaction flask is equipped with a cooling bath, air stirrer, gas addition tube, and thermometer probe. The flask is purged with nitrogen, then charged $AlCl_3$ (1025 g, 7.69 moles) and $CHCl_3$(6.6 L, 16.5 vol.). After cooling the mixture to 0-5 °C, it is charged with 2-thiophene carbonitrile (400 g, 3.66 moles) dropwise via an addition funnel over 10-15 minutes while maintaining the temperature at ≤ 10 °C. The mixture is charged with Cl_2 gas (300g, 4.23 moles, 1.16 EQ) subsurface at ≤ 10 °C over 1.25 hours. The progress of the reaction is monitored by GC, wherein the GC sampling method is quenching an aliquot of the reaction mixture into 6N HCl, extracting with EtOAc, drying over Na_2SO_4, filtering, and injecting the filtrate.

When the reaction is deemed complete by GC analysis [the reaction was deemed complete when the ratio of (sm : prod : dichloro) was approximately (1 : 5.8 : 1) by area % GC.], 6N HCl (8.0 L) is added dropwise via addition funnel over 1.5 hours, while maintaining the temperature at ≤ 20 °C [The HCl addition is extremely exothermic and evolves gas]. The reaction is transferred to a separatory funnel and the layers are separated. After extracting the aqueous layer with $CHCl_3$ (4.0 L), the chloroform layers are combined and washed with de-ionized H_2O (6.0L). The organic layer is dried over Na_2SO_4, filtered and concentrated under vacuum to give a pale yellow semi solid 575g, 109.3%). GC (60°C to 280°C temperature gradient) Area-% analysis shows ~68%

product (t_{ret} = 6.5 min) with major impurities being the unreacted starting material (t_{ret} = 5.1 min) and the dichlorinated product (t_{ret} = 7.4 min). GC Method: Column: DB1; $T_{injecyt}$ = 300 °C ; $T_{initial}$ = 60 °C, t = 2.0 min; T_{final} = 280 °C, rate = 18 °C/min.

B. 4-Chloro-2-thiophene carboxamide.

A 12-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with KOH (288.6 g, 5.143 moles) and De-ionized H_2O (6.04 L) to form a solution that exotherms to ~31 °C. After allowing the solution to cool to ~28.0 °C, th mixture is charged with 4-chloro-2-thiophene carbonitrile (671.3 g, 4.675 moles)[1] followed by EtOH (675 mL). A gradual exotherm occurs upon the addition of EtOH and continues over 1-1.5 hours to ~38 °C. The reaction is stirred at ambient temperature overnight.

The reaction mixture is filtered under vacuum, washed with de-ionized H_2O and dried to give crude product. The solids are dissolved in EtOAc (10.0 L) treated with Na_2SO_4 and Darco for 1-2 hours; then, filtered and washed with EtOAc. The filtrate is concentrated on the Büchi until solids began to precipitate out at 45 °C at which time the vacuum is released, and the temperature is increased to 60-65 °C to redissolve the solids. With stirring at 60 °C, heptane (3.5 L) is added slowly to precipitate solids. After stirring for 15-20 minutes at 60 °C, the mixture is cooled to 30-40 °C and filtered. The solids are washed with heptane (2 x 0.75 L), and dried to give the title compound (t_{ret} = 9.9 min) as a white solid (235.4 g, 31.2 % 96.4 area % by GC analysis). A second crop is obtained from the filtrate to give 67.8 g, 9.0 %; 94.5% area-% by GC analysis). The Overall yield is 303.2 g, 40.1 %.

C. 4-Chloro-N-dimethylaminomethylene-2-thiophene carboxamide.

A 5-L reaction flask equipped with a heating mantle, air stirrer, Dean-Stark apparatus, and thermometer probe is charged with 4-chloro-2-thiophene carboxamide. (300 g, 1.856 moles) and dimethylformamide dimethylacetal (872 mL) to form a slurry that endotherms 1-2 °C from 22-20 °C. The mixture is heated gradually to 96 °C while collecting the distillate (mostly MeOH). The heating mantle is removed, and the mixture is cooled to $\leq$ 25 °C. De-ionized H_2O (3.0 L) is added via an addition funnel and the

[1] A small amount of solids were undissolved at this point.

temperature is maintained at $\leq$ 35 °C. The reaction mixture is extracted with EtOAc (1 x 3.0 L, 1 x 1.5 L), then combined the organics are washed with de-ionized H_2O (1.5 L). The organic phase is dried over Na_2SO_4, filtered, and concentrated under vacuum to give crude product (400 g).

The crude product is dissolved in EtOAc (320 mL, 0.8 Vol) at 50-60 °C; then, heptane (1700 mL, 4.25 Vol) is added slowly while gradually increasing the temperature to 70 °C. A seed crystal (Lot: PP6-H00086-075-1) is added to the cloudy solution to initiate precipitation. The resulting mixture is stirred to room temperature overnight, then filtered and washed with heptane. The solids are dried to give the title compound (t_{ret} = 13.0 min) as a white solid (329.8 g, 82%; 98.2 % area-% by GC analysis).

D. 5-(4-Chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole.

A 3-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide. (155 g, 0.715 moles) and HOAc (1500 mL) to form a solution. Using an ice-water cooling bath to maintain the temperature at $\leq$ 30 °C, methylhydrazine (33.2 g, 0.721 moles) is added dropwise via an addition funnel over 15-20 minutes to form a light yellow slurry. Gradually, the reaction is heated to 90 °C and held at 90 °C for 30 minutes. After analysis of the mixture by GC, the reaction is cooled to ~70 °C; then, concentrated to a thick oil/slurry. De-ionized H_2O (1.67 L) is slowly added to precipitate solids; then, the mixture is cooled to < 30 °C, filtered and washed with de-ionized H_2O (1.67 L). The wet solids (125.8 g) are re-dissolved in warm MTBE (1.64 L), dried over Na_2SO_4, filtered and concentrated to dryness giving the title compound as a pale yellow solid (85.8 g, 60.1% 91.9 % area % by GC).

E. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole.

A 3-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with 5-(4-Chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole (105.3 g, 0.527 moles), ACN (1053 mL) and HOAc (105 mL) to form a solution. NBS

(103.2 g, 0.580 moles) is added portion-wise over 30-60 minutes while maintaining the temperature at ≤ 31 °C. After stirring for 1 hour[2], GC analysis indicated reaction completion. The reaction mixture is poured into de-ionized H_2O (2.1 L, 20vol), stirred for 30 minutes, filtered, and washed with de-ionized H_2O (2 x 1 L). The product is dried in a vacuum oven at 45 °C overnight to give the title compound as a pale yellow solid (123.0 g, 83.8 %; 96.6 % area-% by GC).

F. 2,6-Dimethyl-imidazo[1,2-*b*]pyridazine.

A 3 neck 1L round bottom flask is charged with 6-methyl-pyridazin-3-ylamine (20 g, 0.18 moles), ethanol 2B (200 mL), and chloroacetone (23.7 g, 20.4 mL, 0.256 moles, 1.4 equiv). The reaction mixture is heated at 70 °C overnight. NaHCO3 (23.2 g, 0.276 moles, 1.5 equiv) is added portion wise. After most of bubbling subsides, the reaction is heated at 100 °C overnight. The solvents are removed in vacuo and the residue is taken up in dichloromethane and filtered through a filter paper. The solvent is again removed in vacuo. The residue is purified using silica gel chromatography with a hexanes:ethyl acetate gradient to obtain the title compound (15.5 g, 57%). ^{1}H-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-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g, 2..17 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-*1H*-[1,2,4]triazole (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) and DMF (6 mL) is de-gassed for 15 minutes with N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) and PPh_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 sat. NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) furnish the title compound (0.29 g, 0.84 mmol, 39%). ^{1}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. for $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; found: 345.2.

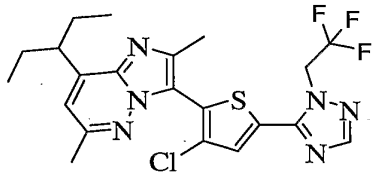
[2] The reaction temperature decreased after 1 hour to 26.7 °C

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.

To a –78 °C solution of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.50 g, 4.35 mmol) and THF (50 mL) is added I_2 (1.21 g, 4.78 mmol). After 10 minutes 2 M LDA (5.44 mL, 10.87 mmol) is added. The solution is stirred for 30 minutes, quenched with water, diluted with EtOAc (100 mL), washed with water (100 mL), sat. $Na_2S_2O_3$ (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (100% EtOAc) furnish the title compound (0.61 g, 1.30 mmol, 30%). ^{1}H NMR ($CDCl_3$) 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. for $C_{15}H_{12}ClIN_6S$ $(M+H)^+$: 471.0; found: 471.0.

Example 234.

Preparation of 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.

To a solution of 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide (1.00 g, 4.62 mmol) and AcOH (1. mL) is added 70 % aqueous 2,2,2-trifluoroethyl-hydrazine (0.79 mL, 4.85 mmol). The solution is heated at 90 °C for 45 minutes, concentrated, dissolved in Et_2O (40 mL), washed with water (30 mL), sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.24 g, 4.62 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 4.88 (q, J = 16.8, 7.8 Hz, 2H), 7.28 (d, J = 0.9 Hz, 1H), 7.31-7.33 (m, 1H), 7.94 (s, 1H). LC/MS (m/z): calcd. for $C_8H_5ClF_3N_3S$ $(M+H)^+$: 268.0; found: 268.0.

B. 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole.

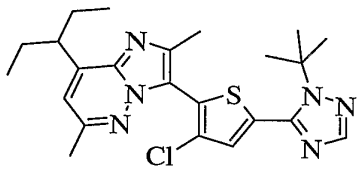
To a solution of 5-(4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (1.13 g, 4.22 mmol) and AcOH (10 mL) in a sealed tube, is added Br_2 (0.23 mL, 4.43 mmol). The solution is heated at 120 °C for 2 hours, and 140 °C for 5 hours. The solution is concentrated, diluted with Et_2O (150 mL), washed with sat $NaHCO_3$ (75 mL), sat. $Na_2S_2O_3$ (75 mL), brine (75 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (5%-15% EtOAc gradient) furnish the title compound (1.04 g, 3.00 mmol, 71%). ^{1}H NMR ($CDCl_3$) δ 4.88 (q, J = 16.0, 7.9 Hz, 2H), 7.22 (s, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_8H_4BrClF_3N_3S$ $(M+H)^+$: 345.9; found: 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), TBABr (0.37 g, 1.14 mmol), and NMP (3 mL), $Pd(OAc)_2$ (0.013 g, 0.057 mmol) and TDBPP (0.037 g, 0.057 mmol) furnish the title compound (0.43 g, 0.89 mmol, 78%). ^{1}H NMR ($CDCl_3$), 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. for $C_{21}H_{22}ClF_3N_6S$ $(M+H)^+$: 483.1; found: 483.2.

Example 235.

Preparation of 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]triazole.

Using a procedure analogous to Example 234A, 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide (5.00 g, 23.07 mmol) and AcOH (50.

mL), *tert*-butylhydrazine hydrochloride (3.16 g, 25.38 mmol) furnish the title compound (0.20 g, 0.83 mmol, 3.6%). ^{1}H NMR ($CDCl_3$) 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. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-^{1}*H*-[1,2,4]triazole.

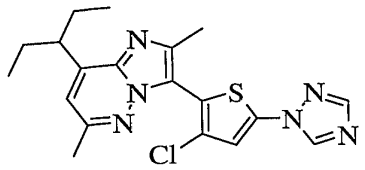
Using a procedure analogous to Example 249B, 1-*tert*-butyl-5-(4-chloro-thiophen-2-yl)-^{1}*H*-[1,2,4]triazole (0.20 g, 0.83 mmol), AcOH (3 mL) and Br_2 (0.051 mL, 0.99 mmol) furnish the title compound (0.27 g, 0.83 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 9H), 7.42 (s, 1H), 8.08 (s, 1H). LC/MS (m/z): calcd. for $C_{10}H_{11}BrClN_3S$ $(M+H)^+$: 320.0; found: 320.0.

C. 3-[5-(2-tert-Butyl-2*H*-[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, 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)-^{1}*H*-[1,2,4]triazole (0.20 g, 0.82 mmol), KOAc (0.34 g, 3.42 mmol), TBABr (0.22 g, 0.68 mmol), and NMP (3 mL), $Pd(OAc)_2$ (0.0077 g, 0.034 mmol) and TDBPP (0.022 g, 0.034 mmol) furnish the title compound (0.039 g, 0.085 mmol, 13%). ^{1}H NMR ($CDCl_3$), 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. for $C_{23}H_{29}ClN_6S$ $(M+H)^+$: 457.2; found: 457.3.

Example 236.

Preparation of 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.



A. 3-(3-Chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

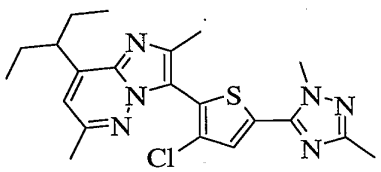
To a solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (2 g, 6 mmol) in 10 mL of anhydrous CH_3CN under nitrogen was added portionwise NIS (1.6 g, 7.2 mmol). The reaction mixture is stirred at reflux for 14 hours. After cooling, the solvent is concentrated under vacuum, the residue is disolved in EtOAc and washed with H_2O, 5% solution of sodium bisulfite, H_2O and brine. The organic layer is dried over magnesium sulfate, filtered and concentrated under vacuum. The crude residue is purified by silica gel chromatography using hex/EtOAc 8:2 as eluent mixture, to obtain 2.4 g (90%) of the title compound; mass spectrum 460 (M+1); ^{1}H-NMR ($CDCl_3$, 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.

To a solution of 3-(3-chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.65 mmol), *1H*-triazole (0.047 g, 0.69 mmol), CuI (0.0062, 0.033 mmol), Cs_2CO_3 (0.45 g, 1.37 mmol) and DMF (3 mL) is added (*1S, 2S*)-(+)-*N,N'*- dimethylcyclohexane-1,2-diamine (0.014 mL, 0.098 mmol). The solution is heated at 112 °C overnight, diluted with CH_2Cl_2 (10 mL) and filtered thru Celite® and concentrated. The residue is purified by ISCO flash chromatography (30%-40% EtOAc gradient furnish the title compound (0.028 g, 0.070 mmol, 11%). ^{1}H NMR ($CDCl_3$) 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. for $C_{19}H_{21}ClN_6S$ $(M+H)^+$: 401.1; found: 401.2.

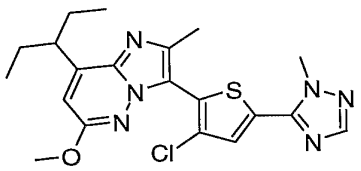
Example 237.

Preparation of 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.



To a –78 °C solution of 3-[3-chloro-5-(2-methyl-2*H*-[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) is added 1.7 M *tert*-BuLi (0.47 mL, 0.80 mmol). After 15 minutes MeI (0.052 mL, 0.83 mmol) is added and the solution warmed to ambient temperature. The solution is diluted with EtOAc (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The solution is recrystalized from acetone: hexane furnish the title compound (0.13 g, 0.30 mmol, 42%). ^{1}H NMR ($CDCl_3$) 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. for $C_{21}H_{25}ClN_6S$ $(M+H)^+$: 429.2; found: 429.2.

Example 238.Preparation of 3-[3-Chloro-5-(2-methyl-2*H*-[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, 69. 18 mmol) is mixed with 2,2-dimethyl-propionamide (8.40 g, 83.01 mmol), BINAP (2.15 g, 3.46 mmol), Cs_2CO_3 (33.8 g, 103.77 mmol) in 1,4-dioxane (150 mL). It is degassed by passing N_2 through for 10 min at rt. $Pd_2(dba)_3$ (3.16 g, 3.46 mmol) is added and the resulting mixture is refluxed overnight. The mixture is cooled to rt, diluted with EtoAc (150 mL); filtered through silica gel; washed with EtOAc (2 x 150 mL). The filtrate is washed with H2O (2 x 300 mL); dried with $MgSO_4$; filtered and concentrated. Purification of the crude material by silica gel chromatography gives the title compound (6.59 g, 31.53 mmol, 46%). 1H NMR (CDCl3): δ. 1.35 (s, 9H), 4.08 (s, 3H), 7.01 (d, J = 9.7 Hz, 1H), 8.41 (d, J = 9.7 Hz, 1H), 8.44 (bs, 1H). ES-MS (m/z): calcd for $C_{10}H_{15}N_3O_2$ $(M+H)^+$: 210.3; found : 210.1.

B. N-[4-(1-Ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide.

Using a procedure analogous to Example 6a, from N-(6-methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide (6.09 g, 29.14 mmol) and a Grignard reagent prepared from 3-pentyl bromide (18.1 mL, 160.3 mmol) and Mg (3.84 g, 160.26 mmol) gives 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 for $C_{15}H_{25}N_3O_2$ $(M+H)^+$: 280.4; found : 280.2.

C. 4-(1-Ethyl-propyl)-2-methoxy-6-methyl-pyrrolo[1,2-b]pyridazine.

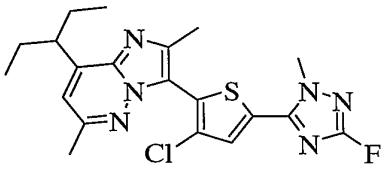
A solution of N-[4-(1-ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide (5.32 g, 19.08 mmol) in EtOH (250 mL) is treated with $ZnCl_2$ (26.0 g, 190.8 mmol) and refluxed for 48 h. The reaction is cooled to rt and concentrated. The residue is taken up with EtOAc (250 mL), and H_2O (100 mL). It is washed with H_2O (2 x 100 mL); dried with Na_2SO_4; filtered and concentrated. The residue is then dissolved in EtOAc (80 mL), reacted with chloroacetone (1.6 mL, 20.03 mmoL) at reflux overnight. While it is hot, $NaHCO_3$ (8.10 g) is added and the reaction is refluxed for 1 h. It is cooled to rt and filtered through silica gel washed with EtOAc and concentrated. Purification of the crude material by chromatography gives the title compound (0.48 g, 2.07 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 for $C_{14}H_{20}N_2O$ $(M+H)^+$: 233.3; found : 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.

A solution of 4-(1-ethyl-propyl)-2-methoxy-6-methyl-pyrrolo[*1,2-b*]pyridazine (74.8 mg, 0.32 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^1H-[1,2,4]triazole (107.5 mg, 0.38 mmol), TDBPP (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 purged 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 h. The reaction is cooled to rt, and diluted with EtOAc (10 mL); filtered through silica gel; washed with EtOAc (3 x 30 mL). The filtrate is washed with H2O (3 x 30 m); dried with Na2SO4, filtered and concentrated. Purification of the crude material by silica gel chromatography gives the title compound (0.1062 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 for $C_{20}H_{23}ClN_6OS$ $(M+H)^+$: 431.9; found: 431.3.

Example 239.

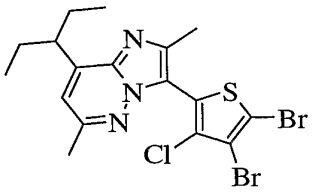
Preparation of 3-[3-chloro-5-(5-fluoro-2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 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) is added 1.7 M *tert*-BuLi (0.47 mL, 0.80 mmol). After 30 minutes the solution is transferred via a cannula into a solution of N-fluorobenzenesulfonamide (0.40 g, 1.25 mmol) and THF. After 30 minutes the solution warmed to ambient temperature. The solution is diluted with EtOAc (40 mL), washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The solution is purified by ISCO (20%-30% EtOAc gradient) furnish the title compound (0.068 g, 0.16 mmol, 16%). ^{1}H NMR ($CDCl_3$) 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. for $C_{20}H_{22}ClFN_6S$ $(M+H)^+$: 433.2; found: 433.2.

Example 240.

Preparation of Preparation of 3-(4,5-dibromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

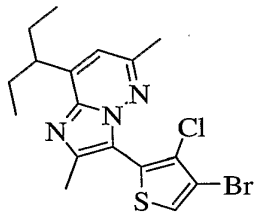


To a solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (5.92 g, 14.34 mmol) and triflouroacetic acid (40 mL) and 98% H_2SO_4 (10 ml) is added NBS (3.83 g, 21.15 mmol). After 10 minutes the solution is poured into ice, and made basic with 5M NaOH. The slurry is extracted with

EtOAc (3 x 100 mL), the combined organic layers washed with water (2 x 400 mL), brine (400 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (6.61 g, 13.44 mmol, 94%). ^{1}H NMR ($CDCl_3$) 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), 6.72 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{18}Br_2ClN_3S$ $(M+H)^+$: 489.9; found: 490.0.

Example 241.

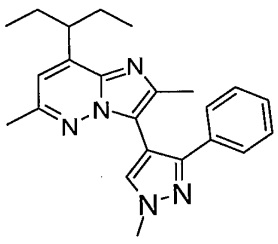
Preparation of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to 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), 1.6 M *n*-BuLi (2.56 mL, 4.09 mmol), and THF (30 mL) furnish the title compound (1.05 g, 2.54 mmol, 68%). ^{1}H NMR ($CDCl_3$) 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. for $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.0; found: 412.1.

Example 242.

Preparation of 3-(1-methyl-3-phenyl-^{1}*H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 1-methyl-3-phenyl-^{1}*H*-pyrazole and 1-methyl-5-phenyl-^{1}*H*-pyrazole.

Sodium hydride (60% dispersion in mineral oil, 0.83 g, 20.8 mmol) is suspended in THF (45 ml) and stirred under a nitrogen atmosphere. 3-Phenyl pyrazole (2.5 g, 17.3 mmol dissolved in THF, 15 ml) is added slowly, stirred for 30 minutes then iodomethane (1.3 ml, 20..8 mmol) added and stirred for 3 hrs. The reaction is added to water and extracted twice with ethyl acetate. The combined organic extracts are ished with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 40% ethyl acetate in hexane) to elute the title compound. Obtained is a mixture of 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole (2.6g, 95% yield).

B. 4-Bromo-1-methyl-3-phenyl-*1H*-pyrazole and 4-bromo-1-methyl-5-phenyl-*1H*-pyrazole.

The mixture of isomers, 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole (1.0g, 6.3 mmol) and NBS (1.1g, 6.3 mmol) are combined in acetonitrile (25 ml), stirred and heated to 70 °C for 1 hr. 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) to elute 4-bromo-1-methyl-3-phenyl-*1H*-pyrazole (504 mg, 34% yield) and 4-bromo-1-methyl-5-phenyl-*1H*-pyrazole (295 mg, 20% yield), respectively:

^{1}H NMR: (400 mHz, DMSO): δ 8.01 (s, 1H), 7.95 (d, 2H), 7.41 (t, 2H), 7.38 (d, 1H), 3.85 (s, 3H).
^{1}H NMR: (400 mHz, DMSO): δ 7.63 (s, 1H), 7.50 (m, 5H) 3.77 (s, 3H).

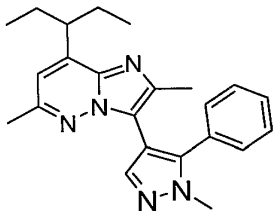
C. 3-(1-Methyl-3-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-3-phenyl-*1H*-pyrazole (250 mg, 1.1 mmol) and cesium carbonate (490 mg, 1.50 mmol) are stirred in DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. $PdCl_2(PPh_3)_2$ (15mg) is added and the mixture is heated to 130^{0}C overnight. The mixture is added to water and extracted twice with ethyl acetate. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude

product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 50% ethyl acetate in hexane) to elute the title compound (17.5 mg, 4% yield). ES-MS (m/z): calc'd for $C_{23}H_{27}N_5$: 373.5; found 374.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.68 (s, 1H), 7.37 (m, 2H), 7.20 (m, 3H), 6.59 (s, 1H), 4.04 (s, 3H), 3.36 (m, 1H), 2.38 (s, 3H), 2.15 (s, 3H), 1.82 (m, 4H), 0.86 (t, 6H).

Example 243.

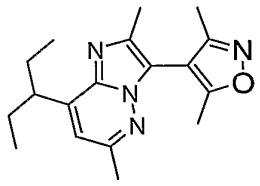
Preparation of 3-(1-methyl-5-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 242, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-5-phenyl-^1H-pyrazole (250 mg, 1.1 mmol), cesium carbonate (490 mg, 1.50 mmol) and $PdCl_2(PPh_3)_2$ (15 mg) in DMF (5 ml) gives the title compound (18 mg, 4% yield). ES-MS (m/z): calc'd for $C_{23}H_{27}N_5$: 373.5; found 374.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.85 (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-dimethyl isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.,

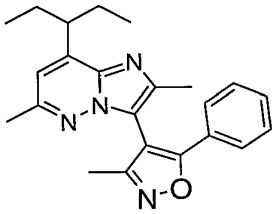


Using the procedure analogous to Example 242, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (200 mg, 0.90 mmol), 4-bromo-3,5-dimethyl

isoxazole (Alfa, 320 mg, 1.8 mmol), cesium carbonate (880 mg, 2.70 mmol) and $PdCl_2(PPh_3)_2$ (25mg) in DMF (5 ml), heated at 130 for 4 hrs, then overnight at ambient temperature gives the title compound (65 mg, 23% yield). ES-MS (m/z): calc'd for $C_{18}H_{24}N_4O$: 312.4; found 313.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 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-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-Bromo-3-methyl-5-phenyl isoxazole.

3-Methyl-5-phenyl isoxazole (Synthesis, **1997**, 439-442) (1.0g, 6.3 mmol) and N-bromosuccinimide (1.2 g, 6.9 mmol) are combined together in acetic acid (30 ml) and heated to reflux with stirring for 2 hrs. The solution is added to water and extracted twice with ethyl acetate. The combined organic extracts are washed with sodium bicarbonate (sat'd) and sat. NaCl then dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 10% ethyl acetate in hexane) to elute the title compound (1.5 g, 100% yield). ^1H NMR (400 mHz, $CDCl_3$): δ 8.02 (m, 2H), 7.49 (m, 3H), 6.34, 2.35 (s, 3H).

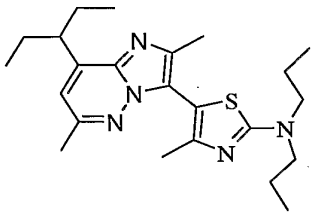
B. 3-(3-Methyl-5-phenyl-isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using the procedure analogous to Example 257, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (200 mg, 0.90 mmol), 4-bromo-3-methyl-5-phenyl isoxazole (430 mg, 1.8 mmol), cesium carbonate (880 mg, 2.70 mmol) and $PdCl_2(PPh_3)_2$ (25mg) in DMF (5 ml) are combined and heated at 130 °C. for 5 hrs to give the title compound (65

mg, 23% yield). ES-MS (m/z): calc'd for $C_{23}H_{26}N_4O$: 374.5; found 375.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 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.

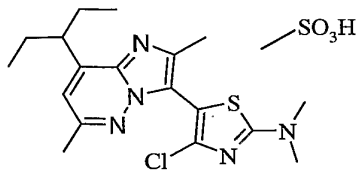
{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dipropyl-amine.



35 mg of 3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.09mmol) and 45 mg of di-n-propylamine (0.44 mmol) and 57 mg of cesium carbonate(0.18 mmol) are place into 4 ml reaction vial with 3 ml of dry THF and the vial is capped with a Teflon cap. The reaction vial is heated at 100°C for 4h. The reaction mixture is transferred into microwave reaction vessel and sealed. The reaction mixture is heated at 160°C for 30 min by microwave. The mixture is concentrated and applied onto silica-gel chromatography column (Hexane:AcOEt=3:1) to give the title compound. 5.3 mg (14%); mass spectrum(m/e): 414; ^1H-NMR($CDCl_3$):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=7.5Hz), 0.89(t, 6H, J=9.4Hz).

Example 247.

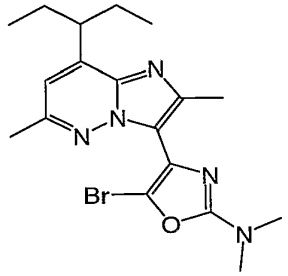
N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-chloro-thiazol-2-yl}-dimethylamine, mesylate salt.



89 mg of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-chloro-thiazol-2-yl}-dimethylamine (0.236 mmol) is dissolved in 2.0 ml of ethylacetate and 0.236ml of 1M methanesulfonic acid in ethylacetate (0.236 mmol) is added. The solvents are removed under N_2 gas and precipitated crystals are collected, washed with Et2O and dried. 92mg (83%); mass spectrum(m/e): 378(M+1); ^{1}H-NMR($CDCl_3$): 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=7.3Hz).

Example 248.

Preparation of {5-Bromo-4-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-oxazol-2-yl}-dimethyl-amine.



A. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-oxazol-4-yl-imidazo[*1,2-b*]pyridazine.

500 mg of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.46 mmol) , 622 mg of oxazole (9.0mmol), 79 mg of triphenylphosphine (0.3 mmol) and 989 mg of cesium carbonate (3.03 mmol) are placed into reaction vial with 7 ml of dry DMF. N_2 gas is bubbled into the mixture for 30 min and 67 mg of Pd_2dba_3 (0.07 mmol) is added. The reaction vial is capped with a Teflon cap and stirred at 130°C for 3 days. The reaction mixture is diluted with dichloromethane, washed with sat NaCl, dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:EtOAc = 3:1) to give the title compound 172 mg (42%); mass spectrum(m/e): 285; ^{1}H-NMR($CDCl_3$): 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-dimethyl-imidazo[*1,2-b*]pyridazine.

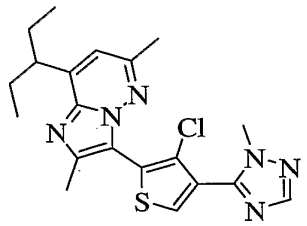
172 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-oxazol-4-yl-imidazo[*1,2-b*]pyridazine (0.60 mmol) and 270 mg of NBS (1.51 mmol) are dissolved in 8.0 ml of dichloromethane and stirred at room temperature overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:EtOAc = 3:1) to give 70 mg of the title compound (26%); mass spectrum(m/e): 442; ^{1}H-NMR($CDCl_3$): 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=7.4Hz).

C. {5-Bromo-4-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-oxazol-2-yl}-dimethyl-amine.

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 carbonate (0.45 mmol) and 3.0 ml of dimethylamine 2.0M in THF (6 mmol) are placed into a 4 ml of reaction vial and the vial is capped 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:AcOE t = 3:1) to give 53 mg of the title compound (87%); mass spectrum(m/e): 406; ^{1}H-NMR($CDCl_3$): 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=7.2Hz).

Example 249.

Preparation of 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.

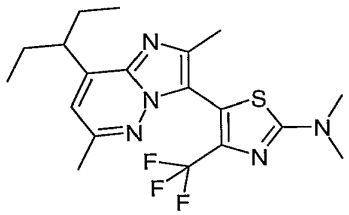


To a flask of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.49 mmol) is added 0.5 g/ mL Reike® Zn (1.3 mL, 0.97 mmol). The slurry is heated at 65 °C for 1 hour, placed in a centrifuge for 5 minutes, and the solution transferred to a flask containing 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 sat. NH_4Cl (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-50% EtOAc gradient) furnish the title compound (0.018 g, 0.043 mmol, 9%). ^1H NMR ($CDCl_3$) δ 0.87 (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), 6.72 (s, 1H), 7.82 (s, 1H), 8.01 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; found: 415.3.

Example 250.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine.



A. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine.

Iodoimidazopiridazine (6.75 g, 19.7 mmol), triphenylphosphine (1.03 g, 3.94 mmol), Cs_2CO_3 (12.84 g, 39.4 mmol) and $Pd_2(dba)_3$ (900 mg, 0.98 mmol) are put into a sealed tube with 65 mL of dry DMF and N_2 gas is bubbled into the mixture for 5 minutes. Thiazole (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 r.t. and quenched by addition of NH_4Cl saturated solution (200 mL). The mixture is extracted with Et_2O (3 x 100 mL) and the organic layers washed with water (2 x 100 mL) and sat. NaCl (100 mL), dried over $MgSO_4$ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent; hexane:EtOAc= 4:1) to give 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.

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 CH_3CN (55 mL) at room temperature is added NBS (5.18 g, 29.1 mmol), and the mixture is stirred at room temperature for 3 hours. A white precipitate is formed that is filtered in vacuo, to give 4.86 g of the title compound (Yield: 84%). ESIMS: m/z 459, 461 $[M+H]^+$.

C. 3-(4-Bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (4.86 g, 10.6 mmol) in THF (150 mL) under N_2 atmosphere at –78°C, BuLi (6.63 mL 1.6 M in hexane, 10.6 mmol) is added dropwise for a period of 10 minutes. The mixture is stirred at –78°C for 30 minutes. Water is added, and the mixture is extracted with Et_2O (3 x 100 mL), dried over $MgSO_4$ and concentrated in vacuo. Crude product is purified by flash chromatography on silica gel (eluent hexane:EtOAc 5:1) to give 3.28 g of the title compound (Yield: 82%). ESIMS: m/z 379, 381 $[M+H]^+$.

D. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.45 g, 6.5 mmol) in NMP (35 mL) in a sealed tube is added $FSO_2CF_2CO_2Me$ (2.5 g, 1.65 mL, 13 mmol) and CuI (2.48 g, 13 mmol). N_2 gas is bubbled into 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 NaCl saturated solution (100 mL) are added to the mixture. The mixture is extracted with Et_2O (5 x 80 mL); washed with water (2 x 100 mL), and dried over $MgSO_4$ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent hexane:EtOAc 5:1) to obtain 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.

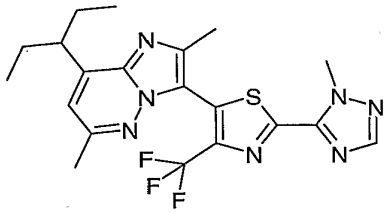
To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine (915 mg, 2.48 mmol) in 40 mL of THF under N_2 atmosphere al –78°C, BuLi (1.86 mL 1.6 M in hexane, 2.98 mmol) is slowly added. The mixture is stirred at –78°C for 30 minutes. Then, a solution of CBr_4 (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 by addition of NH_4Cl saturated solution (50 mL), extracted with Et_2O (2 x 50 mL), dried over $MgSO_4$, and concentrated in vacuo. Crude product is purified by flash chromatography on silica gel (eluent CH_2Cl_2) to obtain 685 mg of the title compound (Yield: 62%). ^1H NMR ($CDCl_3$): δ0.86 (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 of 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 of cesium carbonate (0.66 mmol) are placed in 4 ml reaction vial and 3 ml of dimethylamine 2 M in THF is added. The reaction vial is capped with a Teflon cap and heated at 120°C overnight. The reaction mixture is filtered and concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt =3:1) to give 85 mg of the title compound. Yield 94%. mass spectrum (m/e) : 412 (M+1).

Example 251.

Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-4-trifluoromethyl-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine

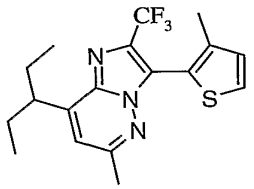


164 mg of 1-Methyl-1,2,4-triazole (1.96 mmol) is dissolved in 2 ml of THF and cooled to –78 °C. 0.8 ml of 2.5M n-butyllithium in hexane (1.96 mmol) is added slowly and stirred at –78 °C, warmed up to room temperature and stirred at r.t. for 15min and

cooled to –78 °C. 3.96 ml of 0.5 M $ZnCl_2$ in THF (1.98 mmol) is added and stirred at room temperature for 15 min. 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) are added. The vial is capped with a Teflon cap and heated at 80 °C overnight. NH_4Cl aq. is added to quench the reaction and the mixture is extracted by CH_2Cl_2, dried over Na2SO4 and evaporated. The crude product is applied onto silica-gel chromatography column (Hexane :AcOEt=3:1) to give 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.



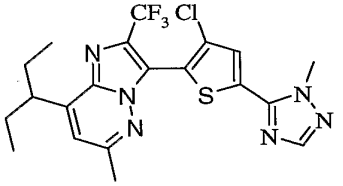
A. 8-(1-Ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

α-Bromotrifluoroacetone (402 mg, 2.93 mmol) is added to a dry 10 mL microwave reaction tube containing 4-(1-ethyl-propyl)-6-methyl-pyridazin-3-ylamine (500 mg, 2.79 mmol) in EtOH (2.0 mL). The resulting mixture is heated at 110 °C in the microwave for 1 hour. $NaHCO_3$ (246.5 mg, 2.93 mmol) is added, and the reaction is mixed well for 5 minutes. Then, the reaction is heated at 110 °C in the microwave for 1 hour. The solvent is removed via reduced pressure, and the reaction is diluted with ethyl acetate (30 mL). The organic layer is washed with H_2O (3 X 10 mL), and the combined aqueous layers are extracted with ethyl acetate (2 X 20 mL). The combined organic extracts are dried over Na_2SO_4, filtered, and purified by silica gel chromatography to give the title compound (29.5 mg, 0.068 mmol, 9.8 %). ^{1}H-NMR ($CDCl_3$), δ 0.87 (t, J = 7.6 Hz, 6H), 1.86 (m, 4H), 2.60 (s, 3H), 3.30 (m, 1H), 6.80 (s, 1H), 8.14 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{13}H_{16}F_3N_3$ $(M+H)^+$: 271.29; found: 272.2

B. 8-(1-Ethyl-propyl)-6-methyl-3-(3-methyl-thiophen-2-yl)-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

To a dry 10 ml round bottom flask with reflux condenser containing 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 Cs_2CO_3 (760 mg, 2.33 mmol) is added NMP (1.7 ml). The mixture is degassed with bubbling N_2 for 15 min and $Pd_2(dba)_3$ (50.8 mg, 0.055 mmol) and PPh_3 (58.2 mg, 0.222 mmol) are added. The reaction mixture is stirred at 130°C overnight. The mixture is cooled to rt, diluted with H_2O; and extracted with EtOAc (3 x 20 ml). The organic layers are dried (Na_2SO_4), filtered and purified by HPLC to give title compound (32 mg, 0.087 mmol, 8%). ^{1}H-NMR ($CDCl_3$), 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 for $C_{18}H_{20}F_3N_3S$ $(M+H)^+$: 367.44; found: 368.1.

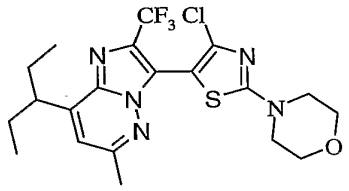
Example 253.Preparation of 3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (182 mg, 0.671 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}*H*-[1,2,4]triazole (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 bubbling nitrogen for 20 minutes. Then, $Pd(OAc)_2$ (8 mg, 0.034 mmol) and TDBPP (20.4 g, 0.34 moles) are added. The reaction mixture is heated to 125 °C for 3 hours to give the title compound (125 mg, 0.267 mmol, 40%). ^{1}H-NMR ($CDCl_3$), δ 0.88 (t, J = 7.2 Hz, 6H), 1.87 (m, 4H), 2.537 (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 for $C_{20}H_{20}ClF_3N_6S$ $(M+H)^+$: 468.93; found: 469.2.

Example 254.

Preparation of 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



A. 8-(1-Ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (460 mg, 1.70 mmol) are dissolved in dry THF (3.5 mL) and cooled to -78°C. A solution of 2.5 M *n*-butyllithium in hexanes (748 µL, 1.87 mmol) is added dropwise. The reaction mixture is stirred for 20 minutes at -78 °C, then warmed to 0 °C for 15 minutes. A solution of I_2 (453 mg, 1.79 moles) in THF (2.0 mL) is added dropwise. The reaction is stirred for 15 minutes at 0 °C, and then warmed to room temp. The reaction is stirred overnight, and the solvent is removed via reduced pressure. The reaction mixture is redissolved in ethyl acetate (50 mL) and washed with a 1 N solution of $Na_2S_2O_3$ (2 X 20 mL). The aqueous layer is extracted with ethyl acetate (2 X 40 mL). The combined organic extracts are dried with Na_2SO_4, filtered, and purified via silica gel chromatography to give the title compound (595 mg, 1.50 mmol, 88%). ^{1}H-NMR ($CDCl_3$), 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 for $C_{13}H_{15}F_3IN_3$ $(M+H)^+$: 397.18; found: 398.3.

B. 2,4-Dichloro-thiazole.

In a 250 mL round bottom flask, 2.4-thiazolidine dione (12.5 g, 107 mmol) is dissolved in phosphorousoxychloride (70 mL) and pyridine (8.5 mL). The mixture is stirred under reflux for 3 hours and cooled to room temp. The reaction mixture is poured into ice water slowly and extracted with dichloromethane. The combined organic extracts are dried with Na_2SO_4, filtered, and concentrated. The residue is purified via silica gel

chromatography to give title compound (9.18 g, 59.6 mmol, 56%). ^{1}H-NMR ($CDCl_3$), δ 7.01 (s, 1H) ppm.

C. 4-(4-Chloro-thiazol-2-yl)-morpholine.

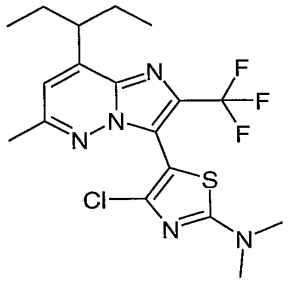
In a 75 mL dry pressure vessel, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and morpholine (560 μL, 6.4 mmol) are dissolved in dry THF (2.0 mL). Cs_2CO_3 (1.56 g, 4.8 mmol) is added, and the reaction vessel is sealed. The reaction mixture is heated to 110 °C overnight. Solvent is removed via reduced pressure, and the crude reaction mixture is purified via silica gel chromatography to give the title compound (597 mg, 2.92 mmol, 91%). ^{1}H-NMR ($CDCl_3$), δ 3.45 (m, 4H), 3.79 (m, 4H), 6.31 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_7H_9ClN_2OS$ $(M+H)^+$: 204.68; found: 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)-morpholine (194 mg, 0.945 mmol), and Cs_2CO_3 (410 mg, 1.26 mmol) are dissolved in DMF. The mixture is degassed with bubbling nitrogen for 15 minutes. Then, $Pd_2(dba)_3$ (18 mg, 0.032 mmol) and PPh_3 (33 mg, 0.126 mmol) are added. The reaction mixture is heated to 130 °C overnight. The reaction is cooled to room temp., quenched with a solution of NH_4Cl sat? (20 mL), and extracted with Et_2O (3 X 50 mL). The combined organic extracts are washed with brine (30 mL), dried with Na_2SO_4, filtered and concentrated. The residue is purified via reverse phase HPLC with a 30-80% gradient of CH_3CN in 10mM NH_4HCO_3/H_2O/5%CH_3CN (pH 10.0)to give the title compound (11 mg, 0.023 mmol, 4%). ^{1}H-NMR ($CDCl_3$), 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 for $C_{20}H_{23}ClF_3N_5OS$ $(M+H)^+$: 473.95; found: 474.2.

Example 255.

Preparation of {4-Chloro-5-[8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine.



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 (a 2.0 M solution in THF, 3 mL, 6.4 mmol) are reacted to give the title compound (60 mg, 0.152 mmol, 15%). ^{1}H-NMR ($CDCl_3$), δ 3.09 (s, 6H), 6.22 (s, 1H) ppm. ES-MS (m/z): calcd for $C_5H_7ClN_2S$ $(M+H)^+$: 162.64; found: 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 coupled with (4-chloro-thiazol-2-yl)-dimethyl-amine (154 mg, 0.945 mmol) to provide desired product. ^{1}H-NMR ($CDCl_3$), 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 for $C_{18}H_{21}ClF_3N_5S$ $(M+H)^+$: 431.91; found: 432.2.

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 ^{125}I-

sauvagine to the cerebellum is then assessed ex vivo as described in Gehlert *et al.* For example, Example 199 provides an ED_{50} result of 1.3 mg/kg.

Example B

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 µl) are set up as follows: 50 µl of ^{125}I-sauvagine (0.2 nM final), 50 µl compound and 100 µl CRF1 membrane (25 µg/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 wash twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried over night and counted with 100 µl Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 µM non-labeled sauvagine. Triplicate determinations are typically run and the median data points plotted by Graph Pad Prism.

Using this assay, the claimed exemplified compounds of the present invention inhibit the binding of ^{125}I-Sauvagine (4 nM) in roller/adherent cells with a Ki (inhibition constant) below 1 µM. For example, Examples 102 and 199 exhibit a Ki of 4.92 ± 0.57 nM and 9.98 ± 0.72 nM, respectively.

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 µl) are set up as follows: 50 ul of ^{125}I-sauvagine (0.2 nM final concentration), 50 µl compound and 100 µl CRF2 membrane (25 µg/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, 1mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried over night and counted with 100 µl Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 µM non-labeled sauvagine. Alternatively, compounds are evaluated using a Scintillation Proximity assay. This assay is set up as follows: 50ul of ^{125}I-Sauvagine (0.2 nM final concentration), 50 µl compound or non-labelled sauvagine (NSB) and 100 µl containing 250 µg wheat germ agglutinin (WGA) SPA beads and CRF2 membrane (1.5 µg/reaction). Plates are incubated for 4-5 hours at room temperature and then centrifuged at 200 X g for 10 minutes. Bound radioactivity is assessed using a Wallac Trilux scintillation counter. Binding is assessed typically using triplicate determinations and the median data points plotted by Graph Pad Prism. Compounds are initially screened at a fixed concentration and, if sufficient activity is noted, subsequent concentration-response curves are generated.

Compounds of the present invention are tested in the CRF2 binding assay and exhibit weak affinity for the CRF2 receptor. For example, Examples 102 and 199 exhibit a percent inhibition at 50 µM of 9.0 ± 2.6 and 16.9 ± 1.9, respectively. These results suggest that the compounds of the present invention are highly selective for the CRF1 receptor.

Example D

Bioavailability and Pharmacokinetic Properties

The compounds of Formula I are antagonists of CRF1, and possess surprisingly useful properties related to their pharmacokinetics and bioavailability.

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: Vdist = amount of drug in the body/ concentration of drug in blood or plasma (Goodman and Gillman's). For a 10 mg 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

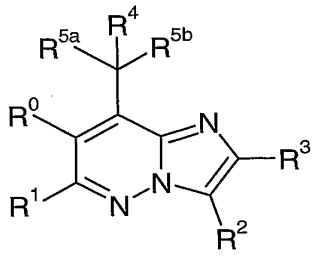
setting, Vdist can be used to determine a loading dose achieve a steady state concentration.

To test for volume of distribution, Male Sprague Dawley rats (N=3) are administered a single 3 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).

An overwhelming 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 L/Kg, respectively, following a single intravenous dose, thiazole Examples 48 and 199 of the present invention exhibits a rat Vdist of only 9 and 2 L/Kg, respectively. Furthermore, thiophene Examples 88 and 39 of the present invention exhibit a rat Vdist of only 44 and 17 L/kg, respectively.

WE CLAIM:

1. A compound of Formula I



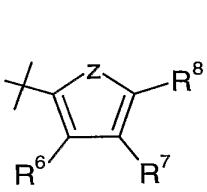
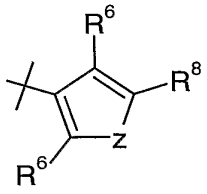
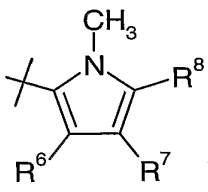
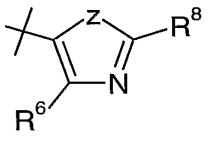
Formula I

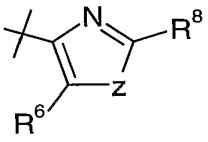
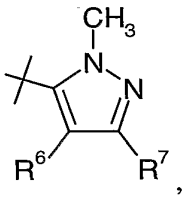
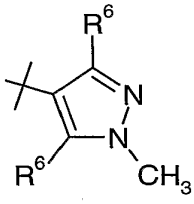
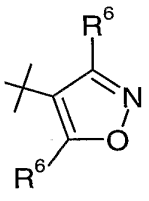
wherein:

R^0 is hydrogen, halo, methyl or ethyl;

R^1 and R^3 are independently methyl, methoxy, or trifluoromethyl;

R^2 is selected from the group consisting of:

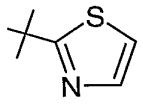
 ,  ,  ,  ,

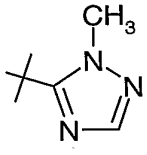
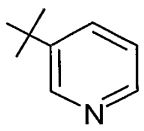
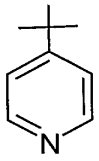
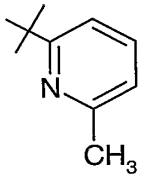
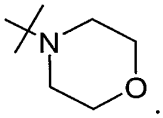
 ,  ,  , and  ;

R^4 is hydrogen, halo, or hydroxy;

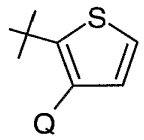
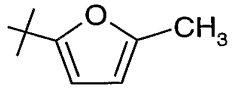
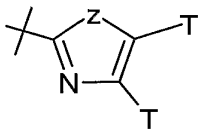
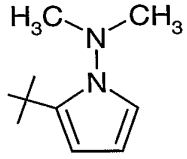
R^{5a} and R^{5b} are independently ethyl or n-propyl;

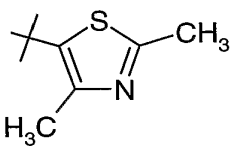
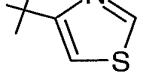
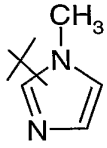
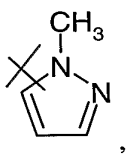
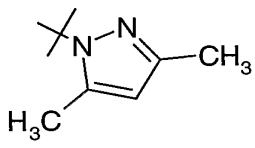
R^6 at each occurrence is independently hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, trifluoromethyl, methoxy, or phenyl;

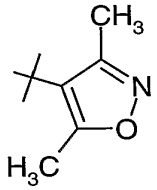
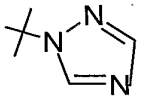
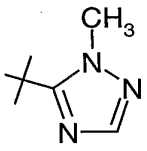
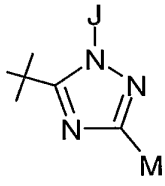
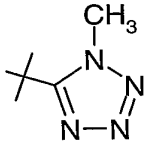
R^7 is hydrogen, halo, methyl, methoxy, dimethylamino,  ,

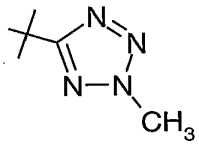
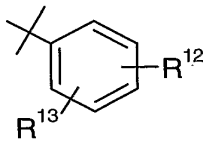
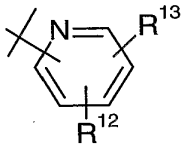
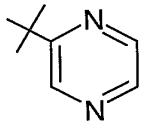
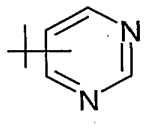
 ,  ,  ,  , or  ;

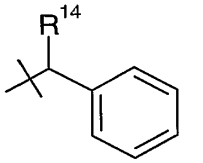
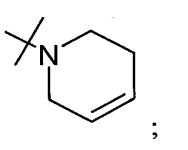
R^8 is selected from the group consisting of hydrogen, halo, cyano, $(C_1$-$C_4)$alkyl, R^aR^bN-, carbamyl, $(C_1$-$C_2)$alkoxy$(C_1$-$C_2)$alkyl, R^{11}-C(O)-,

 ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  , , , ,

, , , , or

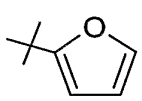
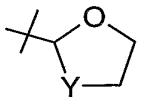
;

R^{11} is methoxy, methylamino, dimethylamino, or phenyl;

R^{12} is hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy dimethylamino, acetyl, or methylsulfonyl;

R^{13} is hydrogen, methyl or halo;

R^{14} is hydrogen or hydroxy;

R^{15} is methylthio, cyclopropyl, phenyl,  or  ;

R^a is hydrogen, $(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_5)$cycloalkyl, methoxy$(C_2\text{-}C_4)$alkyl, acetyl, $(C_1\text{-}C_2)$alkylsulfonyl, (C_3)alkenyl, $R^{15}\text{-}(CH_2)n$-, or $(C_1\text{-}C_2)$alkyl substituted with cyano, formyl, vinyl, or ethynyl;

R^b is hydrogen or $(C_1\text{-}C_3)$alkyl;

X is $-CH_2-$, -CO-, -O-, -S- or $-SO_2-$;

Y is $-CH_2-$ or -O-;

z is S or O;

n is 1 or 2;

Q is hydrogen or methyl;

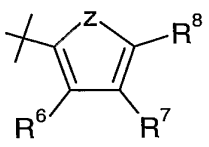
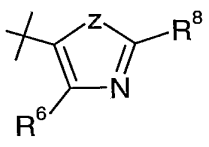
T is hydrogen or methyl;

J is methyl, trifluoroethyl, or tert-butyl; and

M is methyl or halo;

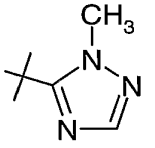
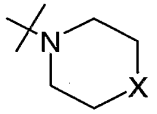
and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 wherein R^0 and R^4 are hydrogen, R^1 and R^3 are methyl, and R^{5a} and R^{5b} are ethyl.

3. The compound according to any one of claims 1 to 2, wherein R^2 is selected from the group consisting of  or  and where z is S.

4. The compound according to any one of claims 1 to 3, wherein R^7 is hydrogen.

5. The compound according to any one of claims 1 to 4, wherein R^6 is halo or methyl.

6. The compound according to any one of claims 1 to 5, wherein R^8 is  or  and where X is O.

7. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

8. A compound according to any one of Claims 1 to 6 for use as a medicament.

9. Use of a compound according to any one of Claims 1 to 6 for the manufacture of a medicament for treating anxiety, depression, major depressive disorder, alcohol withdrawal symptoms, or irritable bowel syndrome in a mammal.

10. Use of a compound according to Claim 9 wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009942

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025 A61P25/20

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 364 952 A (EISAI CO., LTD) 26 November 2003 (2003-11-26) examples	1-10
A	WO 97/29109 A (JANSSEN PHARMACEUTICA N.V; NEUROCRINE BIOSCIENCES INC; CHEN, CHEN; WEB) 14 August 1997 (1997-08-14) examples	1-10
A	EP 1 466 527 A (SUMITOMO CHEMICAL TAKEDA AGRO COMPANY, LIMITED) 13 October 2004 (2004-10-13) examples	1-10

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2006	16/08/2006

Name and mailing address of the ISA/	Authorized officer
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	Menegaki, F

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009942

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOREAU S ET AL: "Synthesis and anticonvulsant Properties of Triazolo- and Imidazopyridazinyl Carboxamides and Carboxylic Acids" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 6, no. 7, July 1998 (1998-07), pages 983-991, XP002991062 ISSN: 0968-0896 compounds 9,10,11 -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/009942

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1364952 A	26-11-2003	WO 02062800 A1	15-08-2002
		US 2004082781 A1	29-04-2004
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
		CN 1205009 A	13-01-1999
		CZ 9802445 A3	14-10-1998
		DE 880523 T1	04-07-2002
		EA 980394 A1	29-10-1998
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		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
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		NO 981357 A	03-08-1998
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EP 1466527 A	13-10-2004	BR 0306810 A	26-10-2004
		CN 1617666 A	18-05-2005
		WO 03061388 A1	31-07-2003
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(71) Applicant: **BRISTOL-MYERS SQUIBB PHARMA COMPANY** [US/US]; Patent Department, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

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

(74) Agents: **DOLAN, Peter, L.** et al.; Patent Department, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

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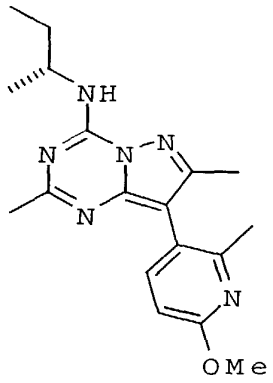
(54) Title: 4-(2-BUTYLAMINO)-2,7-DIMETHYL-8-(2-METHYL-6-METHOXYPYRID-3-YL) PYRAZOLO-[1,5-A]-1,3,5-TRIAZINE, ITS ENANTIOMERS AND PHARMACEUTICALLY ACCEPTABLE SALTS AS CORTICOTROPIN RELEASING FACTOR RECEPTOR LIGANDS



(I)

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

WO 02/072202 A1

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

Field of the Invention

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

Background of the Invention

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Summary of the Invention

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

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

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

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

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

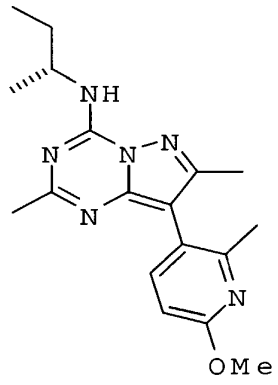
The use of competitive binding assays is considered particularly valuable for screening candidates for new drugs, e.g. to identify new CRF ligands or other compounds having even greater or more selective binding affinity for CRF receptors, which candidates would therefore be potentially useful as drugs.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

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

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

Detailed Description of the Invention

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



(I)

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

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

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

said compound is substantially free of its (S) stereoisomer

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

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

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

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

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

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

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

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

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

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

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

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

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

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

b) detecting the labelled compound bound to the tissue.

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

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

a) a packaging material;

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

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

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

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

Definitions

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

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

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

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

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

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

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

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

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

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

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

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

Syntheses

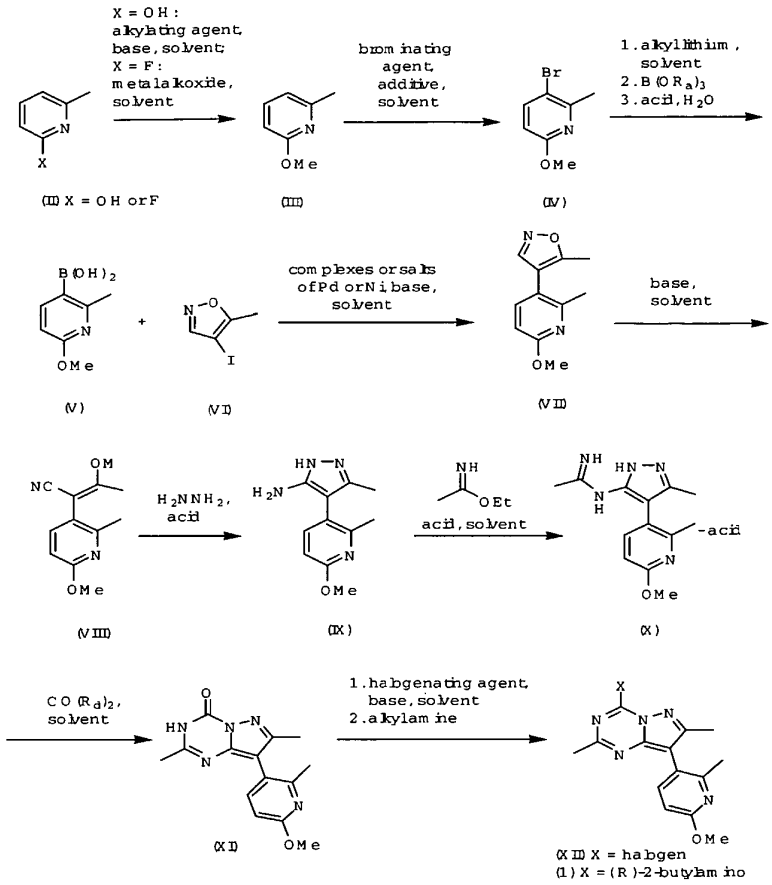
Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes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

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

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

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

Scheme 1



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLES

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

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

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

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

EXAMPLE 1

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

A. 2-Methoxy-6-methylpyridine.

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

B. 2-Methoxy-6-methylpyridine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLE 2

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

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

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

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

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

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

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

Utility

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

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

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

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

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

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

In vivo Biological Assay

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Capsules

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

Soft Gelatin Capsules

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

Tablets

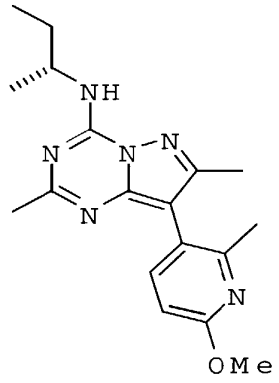
A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase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

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

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

What is claimed is:

1. A compound of Formula (I):



(I)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

b) detecting the labelled compound bound to the tissue.

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

17. An article of manufacture comprising:

a) a packaging material;

b) a compound of claim 1; and

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

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

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Authorized officer
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Telephone No. 703-308-1235

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(71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; Chestnut Run Plaza, 974 Centre Road, Wilmington, 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 Company, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).

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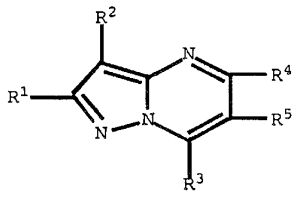

(I)

(57) Abstract

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

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TITLE

PYRAZOLOPYRIMIDINES AS CRF ANTAGONISTS

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

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

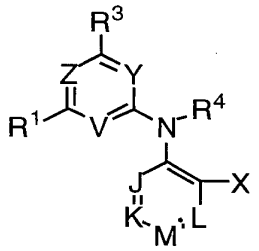
Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton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

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

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

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

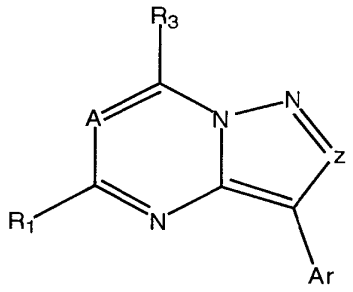
DuPont Merck PCT application US94/11050 describes corticotropin releasing factor antagonist compounds of the formula:



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

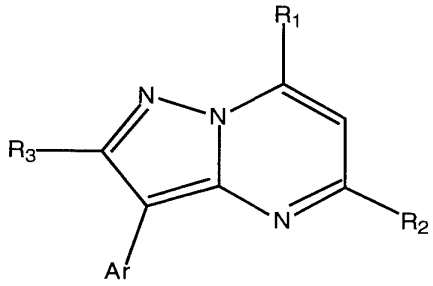
where: V is CR^{1a} or N; Z is CR^2 or N; A is CR^30 or N; and D is CR^{28} or N.

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



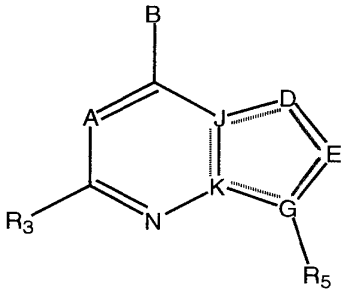
wherein z is N or CR^2 and A is N or CR.

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



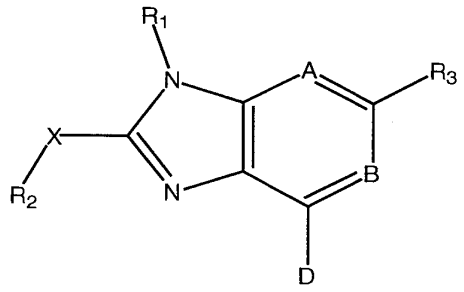
wherein Ar is phenyl, pyridyl and substituted versions thereof.

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



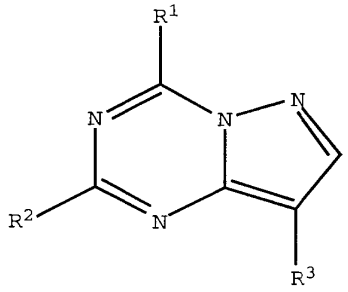
wherein B is selected from a variety of non-aryl groups and R^5 is selected from certain groups such as phenyl or pyridyl or substituted versions thereof.

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



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

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



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

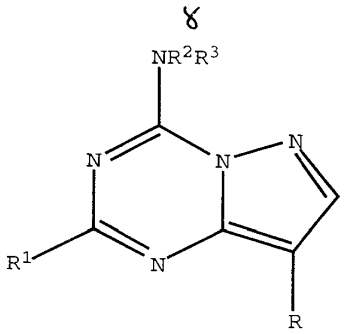
EP 0 594 149 (Ostuka, 1994) discloses pyrazolotriazine and pyrazolopyrimidine compounds of the formula

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

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

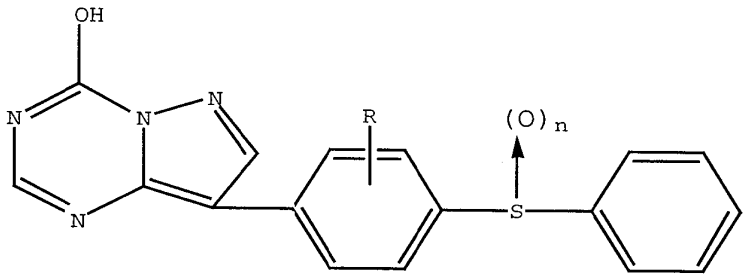
where R1 is CH_3, C_2H_5 or C_6H_5, X is H, C_6H_5, m-$CH_3C_6H_4$, CN, COOEt, Cl, I or Br, Y is H, C_6H_5, o-$CH_3C_6H_4$, or p-$CH_3C_6H_4$, and Z is OH, H, CH_3, C_2H_5, C_6H_5, n-C_3H_7, i-C_3H_7, SH, SCH_3, NHC_4H_9, or $N(C_2H_5)_2$, and states that the compounds are c-AMP phosphodiesterase inhibitors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

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



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

US 5,137,887 discloses pyrazolotriazines of the formula



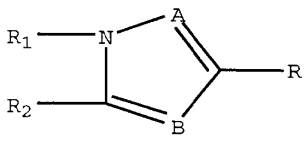
where R is lower alkoxy, and teaches that the compounds are xanthine oxidase inhibitors and are useful for treatment of gout.

US 4,892,576 discloses pyrazolotriazines of the formula

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

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

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



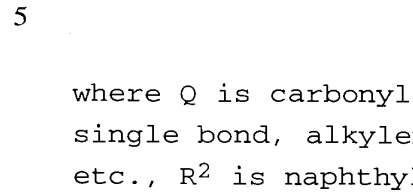
where A can be N, B can be CR_3, R_3 can be phenyl or substituted phenyl, etc., R is $-N(R_4)SO_2R_5$ or $-SO_2N(R_6)R_7$ and R_1 and R_2 can be taken together to form

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

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

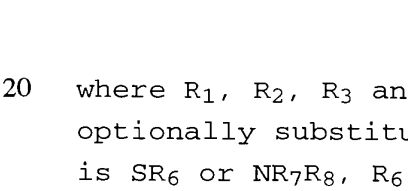
where Z is H, OH, CH_3, C_2H_5, C_6H_5, n-C_3H_7, iso-C_3H_7, SH, SCH_3, NH(n-C_4H_9), or $N(C_2H_5)_2$, R is H or CH_3, and R_1 is CH_3 or C_2H_5. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control,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

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



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

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



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

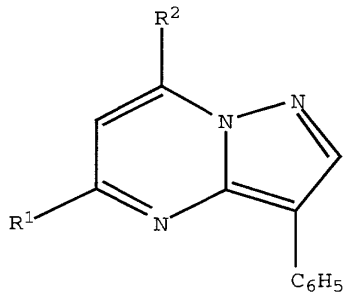
11

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

5

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

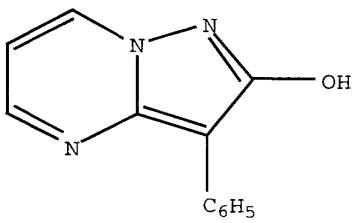
10 Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula



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

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

20



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

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

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

SUMMARY OF THE INVENTION

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

hypersensitivity associated with psychopathological disturbance and stress in mammals.

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

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

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

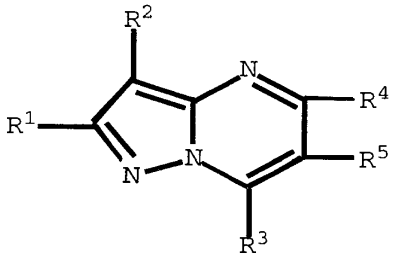
The present invention also relates to the use of a compound of formula I and other compounds generically and specifically disclosed herein in therapy.

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

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

DETAILED DESCRIPTION OF INVENTION

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



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of

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

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

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

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

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

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

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

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

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

$-C(O)OH$,

$-C(O)H$,

$-C(O)Ph$,

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

n is 0, 1 or 2;

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

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

halogen,

$-CN$,

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

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

$-CO_2R^{2f}$,

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

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

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

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

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

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

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

the group R^{2i}, R^{2j}, R^{2k}, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, Br, Cl, F, I, C_{1-4} haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkylOR^{2g}, and C_{3-8} cycloalkyl which is substituted with 0-1 R^{2l} and in wich 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O-, wherein R^{2i} is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl, each R^{2i} being substituted with 0-1 OR^{2m} and 0-5 substituents independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{20}R^{2p}$, $-NR^{2g}CO_2R^{2n}$, $-NR^{20}R^{2p}$ and $-CONR^{20}R^{2p}$;

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

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

wherein

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(f) no entry

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

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

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

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

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

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

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

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

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

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

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

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

(t) in a compound of formula I, R^2 is $C(O)NH_2$, R^1 is CH_3, R^3 is m-CF_3Ph, R^4 and R^5 are H (reg. ref. 47);

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

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

(w) no entry

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

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

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

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

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

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

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

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

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

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

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

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

(jj)-(mm) no entry

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(hhh) in a compound of formula I, R^2 is CN, R^1 is CH_3, R^3 is m-CF_3Ph, R^4 and R^5 are H (reg. ref. 172);

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

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

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

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

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

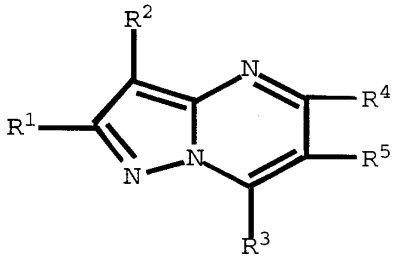
(nnn) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is m-CF_3-Ph, R^4 is H and R^5 is CH_3 (reg. ref. 178);

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

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

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

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



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of

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

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

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

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

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

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

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

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

n is 0, 1 or 2;

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

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

-CN,

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

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

$-CO_2R^{2f}$,

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

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

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

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

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

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

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

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

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

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

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

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

wherein

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

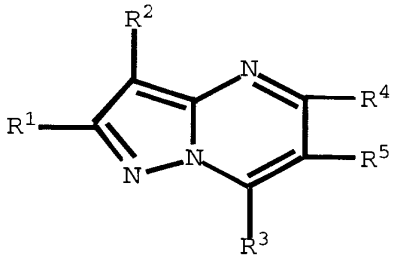
[5] The present invention preferrably relates to a compound as described directly above in groups [1'] and [1]-[4] wherein R^3 is selected from 2,4-dichlorophenyl, 2-chloro-4-methoxyphenyl, 2,4,6-trimethylphenyl, 2,4,6-trimethoxyphenyl, 2-dimethylamino-4-methyl-pyridin-5-yl, 2,4-dichloro-5-fluorophenyl,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

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

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

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

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



(I)

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

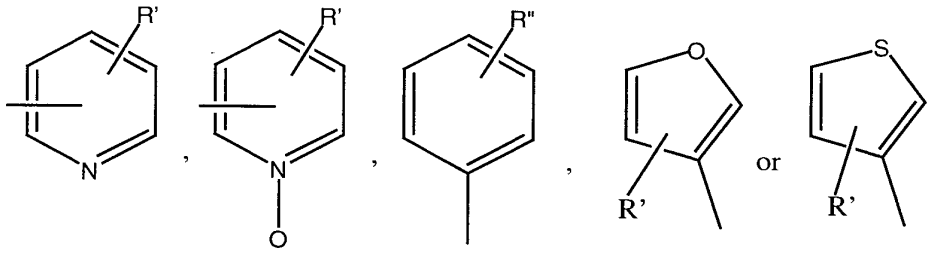
R^1 is selected from C_{1-6} alkyl, C_{1-6} alkyloxy, -SH or OH;

R^2 is selected from C_{1-4} alkyl which is unsubstituted or substituted with 1-4 substitutents selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} 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, $S(O)_nC_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, C_{1-6} alkyl or $NR^{2g}R^{2h}$ wherein R^{2g} and R^{2h} are independently selected from H or C_{1-6} alkyl;

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

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



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

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

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

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

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

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

R^1 is selected from the group consisting of

C_{1-6} alkyl,

C_{2-10} alkenyl,

C_{2-10} alkynyl,

C_{3-6} cycloalkyl,

C_{1-6} alkyloxy,

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

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

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

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

R^2 is selected from the group consisting of

C_{1-10} alkyl,

C_{2-10} alkenyl,

C_{2-10} alkynyl,

C_{3-8} cycloalkyl,

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

C_{1-10} alkyloxy,

C_{1-10} alkyloxyC_{1-10} alkyl,

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

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

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

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

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

- halogen,

-CN,

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

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

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

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

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

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

-C(O)OH,

-C(O)H,

-C(O)Ph,

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

n is 0, 1 or 2;

R^2 is substituted with 0-3 substituents independently

selected from R′, R″, R″′ wherein R′, R″ and R″′ are independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, or

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

halogen,

-CN,

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

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

$-CO_2R^{2f}$,

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

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

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

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

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

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

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

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

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

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

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

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

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

wherein

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

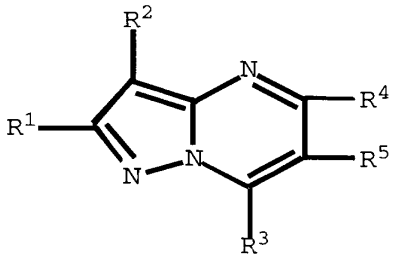
or R^2 is selected from NR'R" wherein R' and R" are independently selected from H or C_{1-6} alkyl.

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

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

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

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



(I)

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

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

R^2 is selected from C_{1-4} alkyl which is unsubstituted or substituted with 1-4 substitutents selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} 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, $S(O)_nC_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, C_{1-6} alkyl or $NR^{2g}R^{2h}$ wherein R^{2g} and R^{2h} are independently selected from H or C_{1-6} alkyl;

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

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

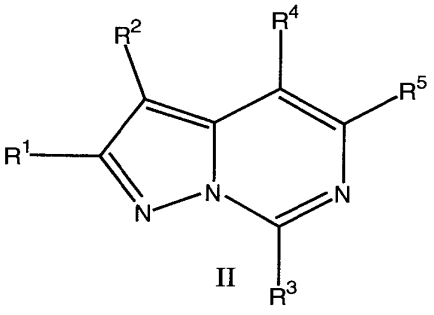
[21] The present invention also relates to a method according to group [19]-[20] wherein R^2 is substituted with 1-4 substituents.

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

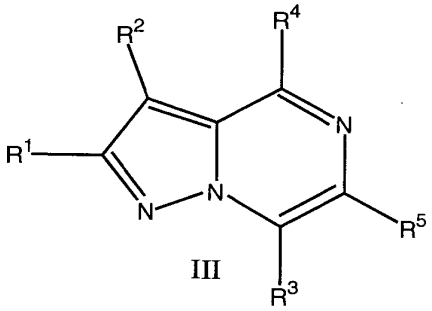
[23] The present invention also provides pharmaceutical compositions comprising compounds of Formula (1) with the variables as recited above in group [1] and [1'] with the proviso that the compounds excluded in proviso (d) in group [1] are included herein and a pharmaceutically acceptable carrier.

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

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



II



III

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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-ethyl-pyrazolo[1,5-a]pyrimidine

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

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

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

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

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

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

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

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

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

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

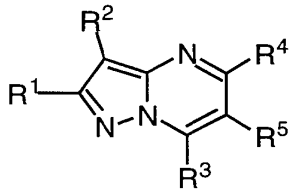
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine

Synthesis

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

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

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



may be prepared according to the following methods:

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

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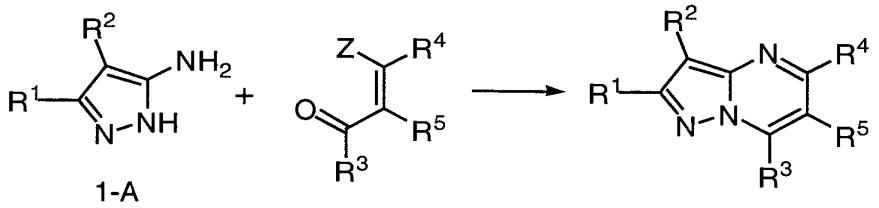
1-B. Here, Z is ethoxy or dimethylamino, and compound 1-B may be prepared by the reaction of a compound of formula $R^3C(=O)CH_2R^6$ with a reagent of formula $R^5C(Z)(OEt)_2$. These types of reactions are normally done by heating the two compounds (as a 1:1 mixture) without solvent, and distilling off 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



1-A 1-B

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

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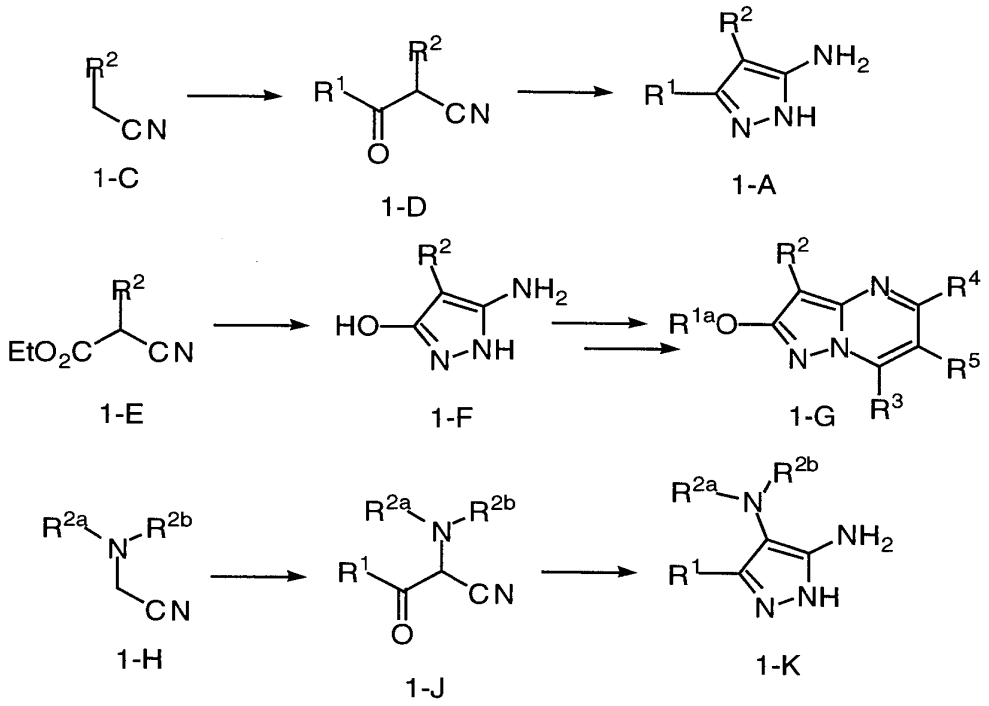
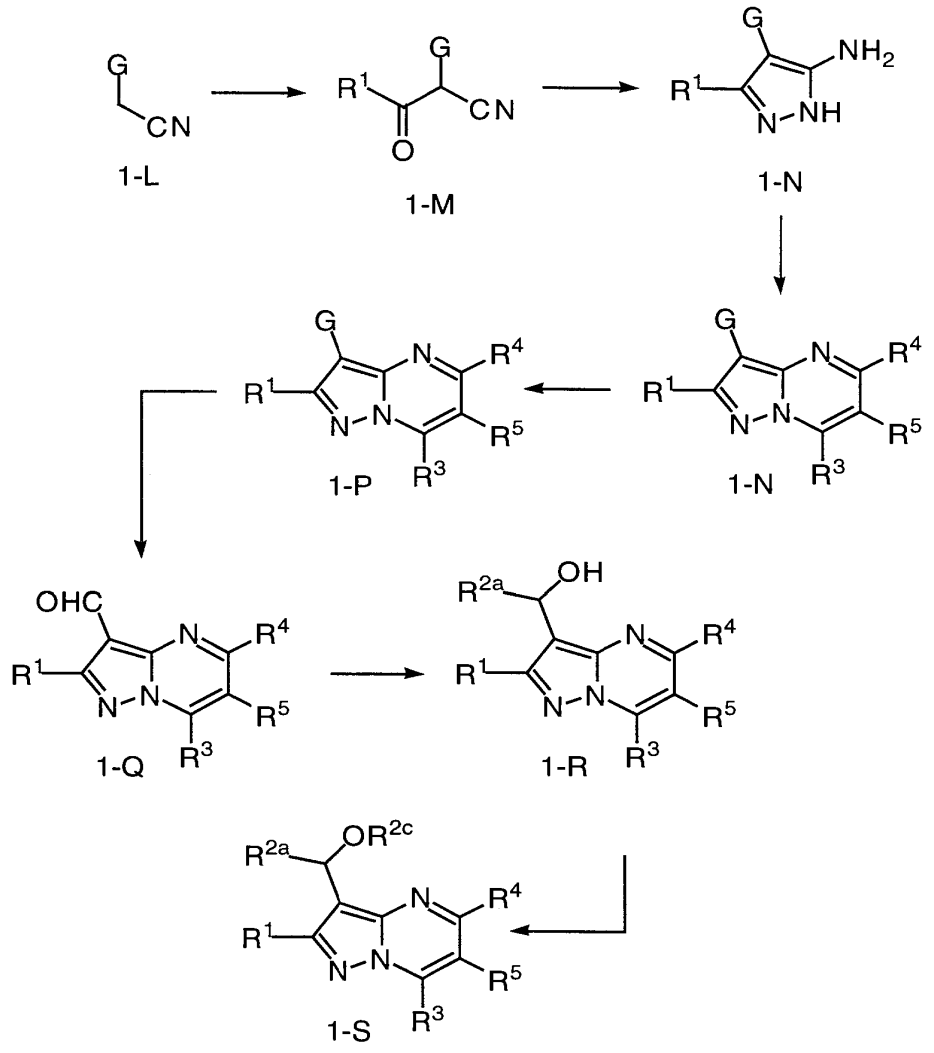
Cyclization with reagent 1-B and O-alkylation with a reagent $R^{1a}X$, wherein X is a halide or pseudohalide group, gives compound 1-G. Finally, strong base treatment of aminonitrile 1-H, usually in the presence of a solvent mixture such as THF/HMPA, followed by acylation and ring-forming, gives diamine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

Scheme 1B



Scheme 1C



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

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

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

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

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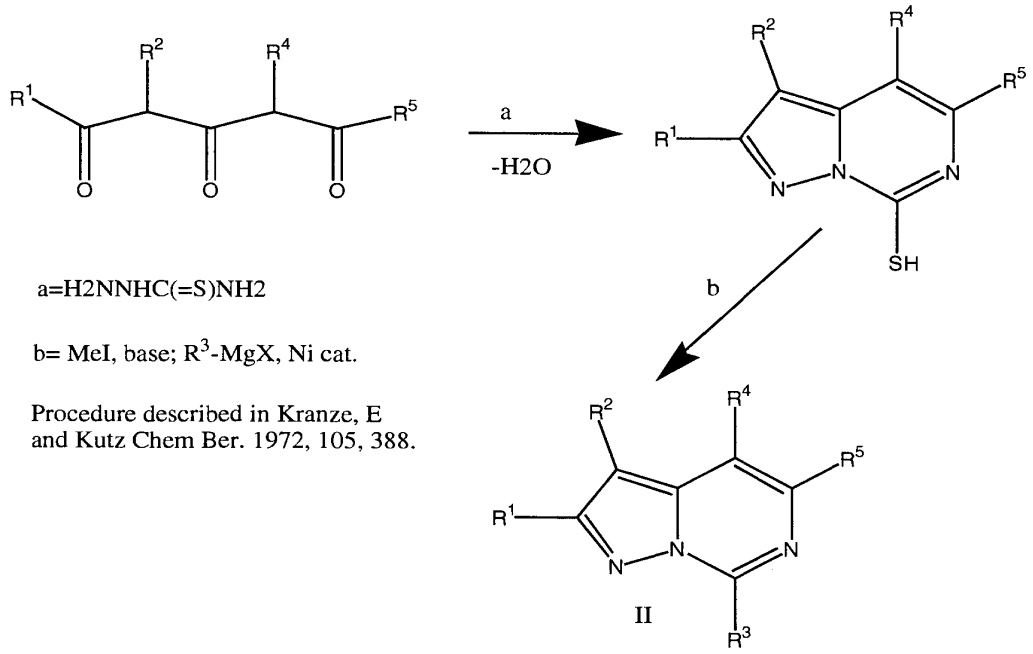
SCHEME 2



a=H2NNHC(=S)NH2

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

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

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

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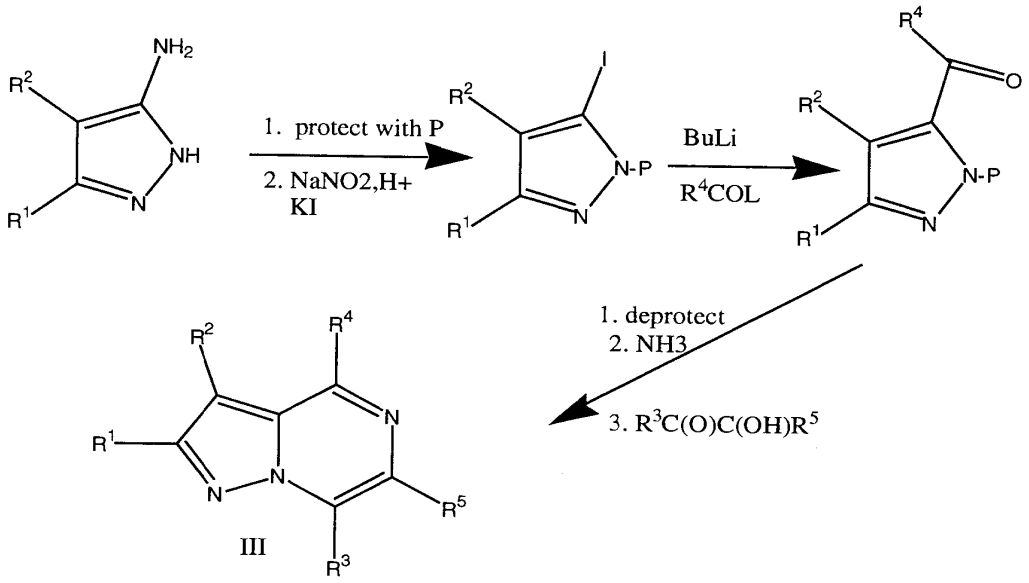
SCHEME 3



III

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

Utility

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

Radioligand binding experiments

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

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

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

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

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

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

In vivo Biological Assay

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Capsules

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

Soft Gelatin Capsules

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

Tablets

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

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

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

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

Examples

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

Example 1

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

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

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

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

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

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

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

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

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

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

Example 31

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

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

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

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

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

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

Examples 51 and 92

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

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

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

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

Part D. A solution of the compound of Example 92 (31 mg, 0.085 mmol) and Proton-Sponge™ (20 mg, 0.093 mmol) in acetonitrile (2 mL) was cooled to 0 °C, and treated with methyl methanetrifluorosulfonate (10 µL, 0.088 mmol). After stirring for 10 hours and warming to ambient temperature, the mixture was evaporated, and the residue was separated directly by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to give the compound of Example 51 as a viscous oil (7 mg, 0.019 mmol, 22%). TLC R_F 0.55 (20:80 ethyl acetate-hexane). Spectral data: ^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 (6H, t, J = 7.4 Hz). MS (NH_3-CI): m/e

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

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

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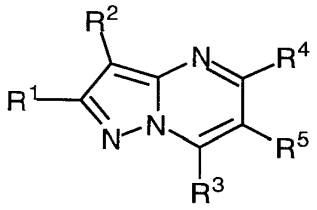
Table 1



Ex No	R^1	R^2	R^4	R^5	R^3	m.p. °C
1	C_2H_5	$(C_2H_5)_2CH$	H	H	2,4-Cl_2-C_6H_3	oil[a]
2	C_2H_5	$(C_2H_5)_2CH$	H	H	2-Cl-4-CH_3O-C_6H_3	88-89
3	C_2H_5	$(C_2H_5)_2CH$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	oil[b]
4	C_2H_5	$(C_2H_5)_2CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	166-167
5	C_2H_5	$(C_2H_5)_2CH$	H	H	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
6	C_2H_5	$(C_2H_5)_2CH$	H	CH_3	2,4-Cl_2-C_6H_3	90-91
7	C_2H_5	$(C_2H_5)_2CH$	H	CH_3	2-Cl-4-CH_3O-C_6H_3	-
8	C_2H_5	$(C_2H_5)_2CH$	H	CH_3	2,4,6-$(CH_3)_3$-C_6H_2	-
9	C_2H_5	$(C_2H_5)_2CH$	H	CH_3	2,4,6-$(OCH_3)_3$-C_6H_2	-
10	C_2H_5	$(C_2H_5)_2CH$	H	CH_3	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
11	C_2H_5	$(C_2H_5)_2CH$	CH_3	H	2,4-Cl_2-C_6H_3	-
12	C_2H_5	$(C_2H_5)_2CH$	CH_3	H	2-Cl-4-CH_3O-C_6H_3	-
13	C_2H_5	$(C_2H_5)_2CH$	CH_3	H	2,4,6-$(CH_3)_3$-C_6H_2	-
14	C_2H_5	$(C_2H_5)_2CH$	CH_3	H	2,4,6-$(OCH_3)_3$-C_6H_2	-
15	C_2H_5	$(C_2H_5)_2CH$	CH_3	H	2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl	-
16	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2,4-Cl_2-C_6H_3	oil[c]
17	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2-Cl-4-CH_3O-C_6H_3	-
18	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2,4,6-$(CH_3)_3$-C_6H_2	oil[d]
19	C_2H_5	$C_4H_9(C_2H_5)CH$	H	H	2,4,6-$(OCH_3)_3$-C_6H_2	-

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

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

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

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

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

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

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

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

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

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

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

Key:

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

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

b) Spectral data for Example 3: ^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 (NH_3-CI): m/e 338 (3), 337 (24), 336 (100). Analysis calc'd for $C_{22}H_{29}N_3$: C, 78.76; H, 8.71; N, 12.53; found: C, 78.74; H, 8.74; N, 12.41.

c) Spectral data for Example 16: ^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 (NH_3-CI): m/e calculated for $C_{21}H_{26}Cl_2N_3$: 390.1504, found 390.1502; 395 (3), 394 (12), 393 (17), 392 (67), 391 (29), 390 (100).

d) Spectral data for Example 18: ^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 (NH_3-CI): m/e calc'd for $C_{24}H_{34}N_3$: 364.2753, found 364.2754; 366 (4), 365 (27), 364 (100).

e) Spectral data for Example 31: ^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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

a]pyrimidine

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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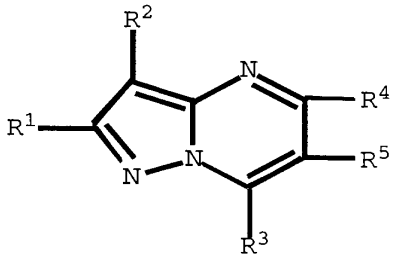
WHAT IS CLAIMED IS:

1. A compound of formula I:



(I)

or a stereoisomer or pharmaceutically accetable salt thereof, wherein:

R^1 is selected from the group consisting of
C_{1-6} alkyl,
C_{2-10} alkenyl,
C_{2-10} alkynyl,
C_{3-6} cycloalkyl,
C_{1-6} alkyloxy,
C_{1-6} alkylS(O)$_n$,
$-NR^{1a}R^{1B}$ wherein R^{1a} and R^{1b} are independently selected from H, C_{1-4} alkyl, $-C(O)C_{1-4}$alkyl,
$-C(O)NR^{1a}R^{1b}$,
$-O-C(O)C_{1-4}$alkyl,
$-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;
X is selected from 0 or S(O)$_n$,
wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl, C_{1-6} alkyloxy, C_{1-4} haloalkyl, $-NR^{1a}R^{1b}$, $-XR^{1c}$;

R^2 is selected from the group consisting of
C_{1-10} alkyl,
C_{2-10} alkenyl,

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C_{2-10} alkynyl,

C_{3-8} cycloalkyl,

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

C_{1-10} alkyloxy,

C_{1-10} alkyloxyC_{1-10} alkyl,

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

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

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

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

- halogen,

-CN,

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

n is 0, 1 or 2;

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

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

halogen,

-CN,

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

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

-CO_2R^{2f},

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

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

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

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

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

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

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

the group R^{2i}, R^{2j}, R^{2k}, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, Br, Cl, F, I, C_{1-4} haloalkyl, -OR^{2g}, -$NR^{2g}R^{2h}$, -C_{1-6} alkylOR^{2g}, and C_{3-8} cycloalkyl which is substituted with 0-1 R^{21} and in wich 0-1 carbons of C_{4-8}

cycloalkyl is replaced by -O-, wherein

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

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

R^{2k} is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for R^{2j}, each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, $-OR^{2m}$,

$-SH$, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group R^{2f}, CO_2R^{2e}, COR^{2e} and SO_2R^{2e};

wherein

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

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

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

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

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

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N_4 in

1-piperiazinyl is substituted with 0-1 substituents selected from the group R^{2t}, CO_2R^{2q}, COR^{2q} and SO_2R^{2q};

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

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

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

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substitued at 0-4 carbon atoms with a substituent independently selected at

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

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

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

(a) a compound of formula I wherein R^1 is unsubstituted, unbranched (linear) C_{1-3} alkyl and R^2 is -C(O)-Ph;

(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$(CH_2)_2$OR, -C(O)O$(CH_2)_2$NHR, or -C(O)O$(CH_2)_2NR^2$ wherein R is C_{1-3} alkyl;

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

(d) a compound of formula I, R^2 is CN, halogen, CO_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$(CH_2)_2$OR, -C(O)O$(CH_2)_2$NHR or -C(O)O$(CH_2)_2NR^2$ wherein R is C_{1-3} alkyl;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(hh) in a compound of formula I, R^2 is CN, R^1 is CF_3, R^3 is m-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 ;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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_3Ph, R^4 and R^5 are H ;

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

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

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

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

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

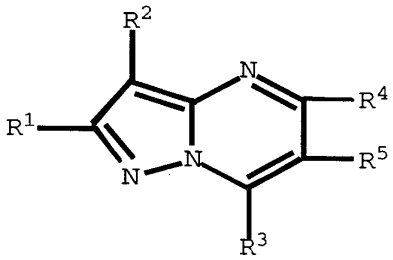
(nnn) in a compound of formula I, R^2 is CN, R^1 is Et, R^3 is m-CF_3-Ph, R^4 is H and R^5 is CH_3 ;

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

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

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

2. A compound of formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of

C_{1-6} alkyl,

C_{2-10} alkenyl,

C_{2-10} alkynyl,

C_{3-6} cycloalkyl,

C_{1-6} alkyloxy,

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

$-NR^{1a}R^{1B}$ wherein R^{1a} and R^{1b} are independently selected from H, C_{1-4} alkyl, $-C(O)C_{1-4}$alkyl, $-C(O)NR^{1a}R^{1b}$, $-O-C(O)C_{1-4}$alkyl, $-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl; X is selected from 0 or $S(O)_n$,

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

R^2 is selected from the group consisting of

C_{1-10} alkyl excluding unsubstituted, unbranched C_{1-3}alkyl,

C_{2-10} alkenyl,

C_{2-10} alkynyl,

C_{3-8} cycloalkyl,

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

C_{1-10} alkyloxy,

C_{1-10} alkyloxyC_{1-10} alkyl,

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

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

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

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

$-NR^{2c}R^{2D}$ wherein R^{2c} and R^{2d} are independently selected from H, C_{1-8} alkyl, $S(O)_nC_{1-4}$ alkyl, $C(O)NR^{2c}R^{2d}$, CO_2C_{1-4}alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxyC_{1-6} alkyl, $-C(O)C_{1-4}$alkyl

or R^{2c} and R^{2d} may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,

n is 0, 1 or 2;

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

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

-CN,

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

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

$-CO_2R^{2f}$,

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

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

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

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

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

1-morpholinyl,

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

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

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

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

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

wherein

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3. The compound according to Claim 1 or 2 wherein

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

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

4. The compound according to Claims 1 or 2 or 3 wherein R^3 is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

5. The compound according to Claims 1,2,3 or 4 wherein R^2 is selected from C_1 alkyl of the formula -CR'R"R"' wherein R', R" and R"' are independently selected from H, C_{1-6} alkyl, C_{3-7} cycloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, with the proviso that each of R',R" and R'" cannot be H;

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

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

7. A compound of formula (I)

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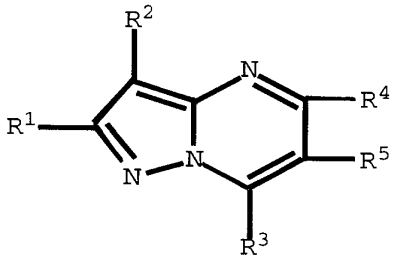


(I)

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

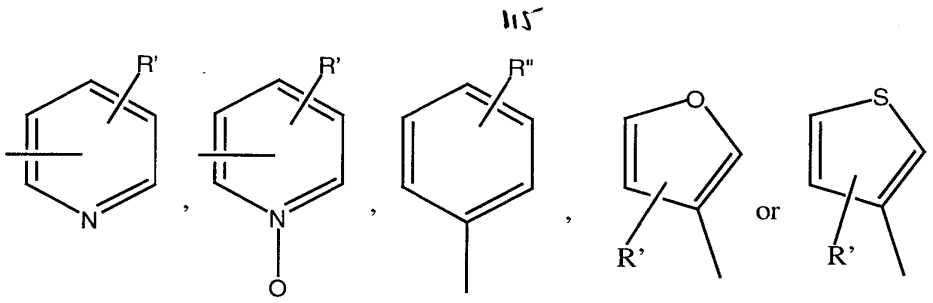
R^1 is selected from C_{1-6} alkyl, C_{1-6} alkyloxy, -SH or OH;

R^2 is selected from C_{1-4} alkyl which is unsubstituted or substituted with 1-4 substitutents selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} 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, $S(O)_nC_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, C_{1-6} alkyl or $NR^{2g}R^{2h}$ wherein R^{2g} and R^{2h} are independently selected from H or C_{1-6} alkyl;

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

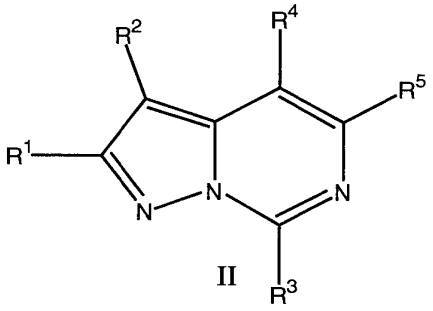
with the proviso that when R^1 and R^2 are unsubstituted, unbranched C_{1-3} alkyl, R^3 may not be



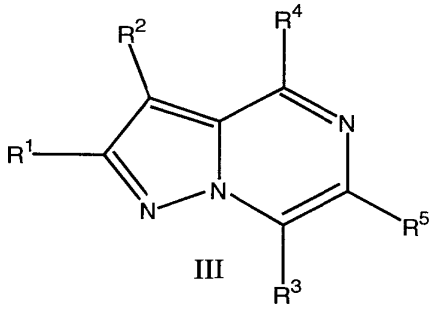
wherein R' is H or C_{1-3} alkyl and R" is H or o-trifluoromethyl, m-trifluoromethyl or m-methoxy.

8. The compound according to Claims 1-7 wherein R^3 is substituted with 2-4 substituents.

9. A compound of the formula:



II



III

or a pharmaceutically acceptable salt or isomer thereof wherein R^1-R^5 and other variables are as defined in claims 1-8.

10. Use of a compound according to Claims 1-9 in therapy.

11. Use of a compound according to Claims 1-9 to antagonize a CRF-1 receptor in mammals including humans wherein binding to the receptor causes and ultimately

results in the treatment of affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of according to Claims 1-9.

12. A pharmaceutical composition comprising a compound according to Claims 1-9 and a pharmaceutically acceptable carrier with the proviso that, in a compound of formula I according to Claim 1, proviso (d) compounds are not excluded.

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(71) Applicants: **NEUROCRINE BIOSCIENCES, INC.** [US/US]; 12780 El Camino Real, San Diego, California 92130 (US). **SANOFI** [FR/FR]; 54 Rue De La Boetie, 75008 Paris (FR).

(72) Inventors: **FARBER, Robert H.**; c/o Neurocrine Biosciences, Inc., 12780 El Camino Real, San Diego, CA 92130 (US). **LOEWEN, Gordon Raphael**; c/o Neurocrine Biosciences, Inc., 12780 El Camino Real, San Diego, California 92130 (US). **ZHANG, Xiaoping**; c/o Neurocrine Biosciences, Inc., 12780 El Camino Real, San Diego, CA 92130 (US). **GIRI, Nagdeep**; c/o Neurocrine Biosciences, Inc., 12780 El Camino Real, San Diego, CA 92130 (US). **CHAN, Jean L.**; c/o Neurocrine Biosciences, Inc., 12780 El Camino Real, San Diego, CA 92130 (US). **STIRN, Scott**; c/o Neurocrine Biosciences, Inc., 12780 El Camino Real, San Diego, California 92130 (US). **SAYERS, Brian**; c/o Neurocrine Biosciences, Inc., 12780 El Camino Real, San Diego, CA 92130 (US). **TAYLOR, Graeme**; c/o Neurocrine Biosciences, Inc., 12780 El Camino Real, San Diego, CA 92130 (US). **COSTA, Christina Marie**; c/o Neurocrine Biosciences, Inc., 12780 El Camino Real, San Diego, CA 92130 (US). **PARKS, Stacy**; c/o Bend Research, Inc., 63045 NE Corporate Pl., Bend, OR 97701 (US). **VICKERY, Anthony D.**; c/o Bend Research, Inc., 63045 NE Corporate Pl., Bend, OR 97701 (US). **DOWNING, Kristie M.**; c/o Bend Research, Inc., 63045 NE Corporate Pl., Bend, OR 97701 (US). **IYOHA, Kingsley**; c/o Quotient Sciences Limited, Trent House, Mere Way, Ruddington, Nottingham, Nottinghamshire NG11 6JS (GB). **NGWENYA-JONES, Ayanda**; c/o Quotient Sciences Limited, Trent House, Mere Way, Ruddington, Nottingham, Nottinghamshire NG11 6JS (GB). **CHARLIER, Anne**; c/o SANOFI, Patent Department, 54 rue de la Boétie, 75008 Paris (FR). **MEHTON, Gurvinder Singh**; Trent House, Mere Way, Ruddington, Nottingham Nottinghamshire NG11 6JS (GB).

(74) Agent: **BOYLE, Craig D.** et al.; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

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(54) **Title:** CRF1 RECEPTOR ANTAGONIST, PHARMACEUTICAL FORMULATIONS AND SOLID FORMS THEREOF FOR THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA

(57) **Abstract:** Provided are methods related to treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1 S)-2-cyclopropyl- 1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-l,3-thiazol-2-amine (Formula 1), or a pharmaceutically acceptable salt thereof. Further provided are pharmaceutical formulations and solid forms of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-l-(3-fluoro-4-methylphenyl)ethyl]-5-mcthyl-N -prop-2 -ynyl-l,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and their use in the treatment of congenital adrenal hyperplasia (CAH).

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CRF1 RECEPTOR ANTAGONIST, PHARMACEUTICAL FORMULATIONS AND SOLID FORMS THEREOF FOR THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA

TECHNICAL FIELD

The present disclosure relates to 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for the treatment of congenital adrenal hyperplasia (CAH). The present disclosure further relates to pharmaceutical formulations and solid forms of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and their use in the treatment of congenital adrenal hyperplasia (CAH).

BACKGROUND

Classic congenital adrenal hyperplasia (CAH) is a disease that includes a group of autosomal recessive disorders that result in an enzyme deficiency that alters the production of adrenal steroids due to 21-hydroxylase deficiency, a condition that results in little or no cortisol biosynthesis. One clinical manifestation of the absence of cortisol is the lack of feedback inhibition of pituitary adrenocorticotropic hormone (ACTH) secretion. Increased ACTH levels cause adrenal hyperplasia and the enzyme mutation causes a shunting of cortisol precursor steroids to alternate pathways. Most notably, the shunting of androgens leads to virilization and other developmental complications in females and the over-accumulation of ACTH is associated with the formation of testicular adrenal rest tumors in males. In addition, since the same enzyme (21-hydroxylase) is used in the pathway for the biosynthesis of the mineralocorticoids, a number of these patients suffer from aldosterone deficiency which can result in dehydration and death due to salt-wasting. The prevalence of classic 21-hydroxylase deficiency CAH in the US general population, based on newborn screening, has been documented as 1:10,000 to 1:20,800 (Trakakis et al., "An update to 21-hydroxylase deficient congenital adrenal hyperplasia," *Gynecol. Endocrinol.* (2010) 26(1):63-71; Hertzberg et al., "Birth prevalence rates of newborn screening disorders in relation to screening practices in the United States," *J. Pediatr.* (2011) 159(4):555-560).

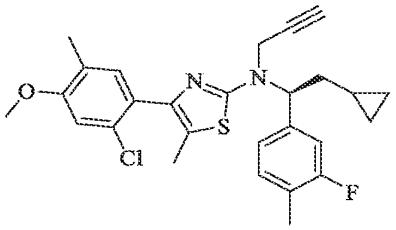
Pediatric patients from birth through adolescence, and females in particular, appear to be the most vulnerable population of CAH sufferers and represent the subgroup of patients with

the greatest unmet medical need (Cheng and Speiser, "Treatment outcomes in congenital adrenal hyperplasia," *Adv. Pediatr.* (2012) 59(1):269-281; Merke and Poppas, "Management of adolescents with congenital adrenal hyperplasia," *Lancet Diabetes Endocrinol.* (2013) 1(4):341-352). Excessive androgen production in these younger patients results in early onset puberty and adrenarche, changes in skeletal maturation patterns, short stature caused by premature growth plate fusion, as well as significant hirsutism and acne problems. While survival is properly ensured through steroid replacement strategies based on physiologic dosing of glucocorticoids (e.g., hydrocortisone) and mineralocorticoids (e.g., fludrocortisone), these doses are often inadequate to suppress the accumulating ACTH and overproduction of progestogens and androgens (e.g., 17-hydroxyprogesterone [17-OHP], androstenedione, and testosterone). The uncontrolled symptoms of androgen excess, indeed, have a substantial impact on the day-to-day functioning and development of these patients.

Currently, exogenous corticosteroids are the standard of care for treating patients with classic CAH. This treatment is used to correct the cortisol deficiency and reduce the excessive ACTH levels and androgen excess. However, the dose and duration of steroid use required to suppress ACTH are typically well above the normal physiological level used for cortisol replacement alone (as in patients with Addison's disease). This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, reduced growth velocity, and decreased bone mineral density in CAH patients (Elnecave et al., "Bone mineral density in girls with classical congenital adrenal hyperplasia due to CYP21 deficiency," *J. Pediatr. Endocrinol. Metab.* (2008) 21(12):1155-1162; King et al., "Long-term corticosteroid replacement and bone mineral density in adult women with classical congenital adrenal hyperplasia," *J. Clin. Endocrinol. Metab.* (2006) 91(3):865-869; Migeon and Wisniewski, "Congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Growth, development, and therapeutic considerations," *Endocrinol. Metab. Clin. North Am.* (2001) 30(1):193-206).

Corticotropin releasing factor (CRF) is a hypothalamic hormone released directly into the hypophyseal portal vasculature and acts on specific corticotropin releasing factor 1 (CRF1) receptors on corticotropes in the anterior pituitary to stimulate the release of ACTH. Blockade of these receptors has been shown to decrease the release of ACTH in both animals and humans. Therefore, compounds that block CRF1 receptors have the potential to directly inhibit the excessive ACTH release that occurs in CAH and thereby allow for normalization of androgen production while using lower, more physiologic doses of hydrocortisone.

The compound of Formula (I)



(I)

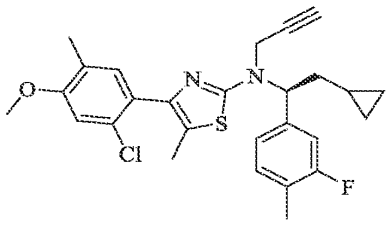
4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, is a selective CRF1 receptor antagonist. The compound of Formula (I) can be prepared according to the methods described in U.S. Patent Nos. 6,586,456 and 8,314,249, each of which is hereby incorporated by reference in its entirety. The compound of Formula (I) is a low solubility compound with low bioavailability. Partially due to its low solubility, attempts at formulating the compound of Formula (I) have proven to be difficult, particularly for formulations suitable for pediatric administration.

Thus, there is a need for a treatment for CAH that avoids the severe complications associated with corticosteroid therapy. There is also a need for a formulation of the compound of Formula (I) with increased bioavailability and a need for a formulation of the compound of Formula (I) that is suitable for pediatric administration. The formulations and methods of the present invention help address these and other needs.

SUMMARY

Provided herein is a pharmaceutical composition comprising:

(a) a compound of Formula (I):



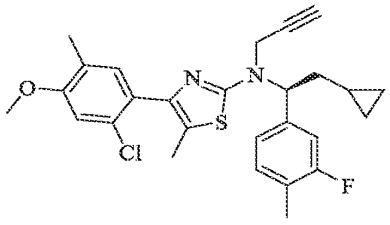
(I)

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

Provided herein is a pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):



(I)

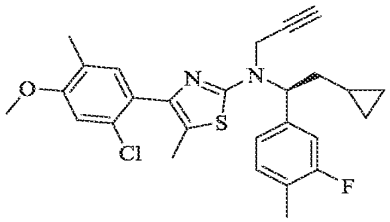
or a pharmaceutically acceptable salt thereof;

(b) one or more of a sweetener, an anti-oxidant, and a flavor; and

(c) a liquid vehicle.

Also provided herein is a pharmaceutical composition of the present disclosure (e.g., a pharmaceutical composition in oral solution dosage form of the present disclosure) for use in therapy, for example, for use in any of the methods disclosed herein.

Provided herein is a method for treating congenital adrenal hyperplasia (CAH) comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject.

Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an

amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

In some embodiments, the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof. In some embodiments, the circadian release occurs between the hours of 2 a.m. and 10 a.m.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25%. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50%.

In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50%.

In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

Provided herein is a method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of androstenedione in the subject. In some embodiments, the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

Also provided herein is a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of androstenedione in the subject.

Also provided herein is use of a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of androstenedione in the subject.

In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

Provided herein is a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-

1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

In some embodiments, the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

Provided herein is a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof. In some embodiments, the corticosteroid is a glucocorticoid.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

Provided herein is a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising

administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side

effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine,

or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

Provided herein is a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the method comprises:

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

In some embodiments, the method further comprises (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i). In some embodiments, the method further comprises (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

In some embodiments, steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

In some embodiments, steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

In some embodiments, step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

In some embodiments, step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

Provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, where in the subject is in a fed state.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method

of treating congenital adrenal hyperplasia (CAH) in a subject, wherein the subject is in a fed state.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject, wherein the subject is in a fed state.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1500 calories per liter with a caloric distribution of about 14.7% protein, about 32% fat and about 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

In some embodiments, administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof when comparing oral administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-

N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the fed and fasting states.

In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

Provided herein is a method of reducing glucocorticoid burden in a subject as measured after a time period of administration of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing glucocorticoid burden in a subject, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing glucocorticoid burden in a subject, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

Provided herein is a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the symptom is improved after a time period of administration of the compound , or pharmaceutically acceptable salt thereof, wherein the improvement in the

one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

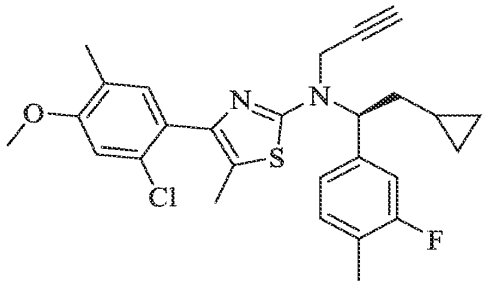
Also provided herein is a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

Also provided herein is use of a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof for use in therapy, for example, for use in any of the methods disclosed herein.

Also provided herein is use of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods disclosed herein.

Also provided herein is a spray-dried dispersion containing 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



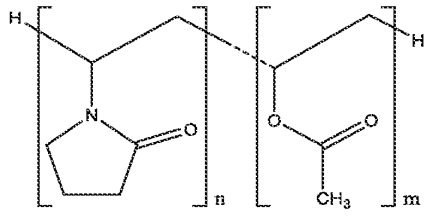
(I)

or a pharmaceutically acceptable salt thereof, and a polymer. In some embodiments, the polymer is selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:9 to about 1:1.

In some embodiments, the polymer is a neutral polymer. In some embodiment, the neutral polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

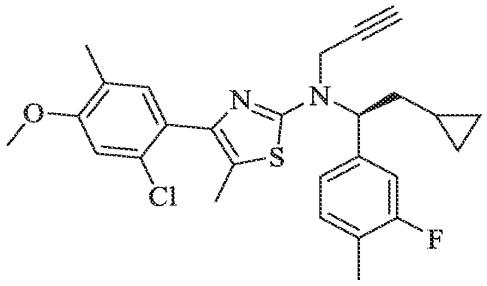
In some embodiments, the polymer is an enteric polymer. In some embodiments, the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer.

In some embodiments, the polymer is a pyrrolidone polymer. In some embodiments, the pyrrolidone polymer is selected from polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone vinyl acetate (PVP/VA). In some embodiments, the pyrrolidone polymer is PVP/VA. In some embodiments, the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 40:60 to about 60:40 by weight. In some embodiments, the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight. In some embodiments, the copolymer has the structure:



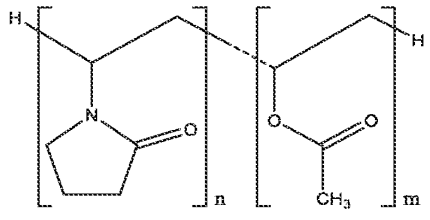
wherein the value of n is about 1 to about 2 times the value of m. In some embodiments, the copolymer is copovidone, wherein the value of n is about 1.16 times the value of m. In some embodiments, the copolymer is copovidone having an average molecular weight of about 45,000 to about 70,000.

Provided herein is a spray-dried dispersion comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



wherein the value of n is about 1 to about 2 times the value of m and the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight; and wherein the weight ratio of the compound of Formula (I) to the copolymer is from about 1:1 to about 1:9.

In some embodiments of the spray-dried dispersions of the present disclosure, the compound of Formula (I) and the polymer together form homogeneous particles. In some embodiments, the particles have a particle size distribution D_{50} of about 5 μm to about 100 μm. In some embodiments, the particles have a particle size distribution D_{50} of about 10 μm to

about 50 μm. In some embodiments, the particles have a particle size distribution D_{50} of about 15 μm to about 30 μm.

In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:1.5 to about 1:9. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:2.5 to about 1:4. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is about 1:3.

In some embodiments, the particles have a residual solvent content less than about 2 wt %. In some embodiments, the particles have a residual solvent content less than about 1 wt %. In some embodiments, the particles have a residual solvent content of about 0.5 wt % or less.

In some embodiments, the compound of Formula (I) in the dispersion is substantially amorphous.

Also provided herein is a method for preparing a spray-dried dispersion of the present disclosure, comprising: dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer.

In some embodiments, the method comprises removing the organic solvent after formation of the spray-dried dispersion by drying the spray-dried dispersion. In some embodiments, the spray-dried dispersion is dried with a convection tray dryer. In some embodiments, the organic solvent is acetone.

In some embodiments, the spray dryer inlet temperature is about 60°C to about 80°C. In some embodiments, the spray dryer inlet temperature is about 72°C.

In some embodiments, the spray dryer outlet temperature is about 25°C to about 45°C. In some embodiments, the spray dryer outlet temperature is about 35°C.

In some embodiments, the homogeneous particles comprise a bulk density of less than about 0.2 g/mL. In some embodiments, the homogeneous particles comprise a bulk density of less than about 0.15 g/mL.

In some embodiments, the homogeneous particles comprise a tapped density of less than about 0.3 g/mL. In some embodiments, the homogeneous particles comprise a tapped density of less than about 0.25 g/mL.

Also provided herein is a pharmaceutical composition comprising the spray-dried dispersion of the present disclosure and one or more pharmaceutically acceptable excipients. In some embodiments, the spray-dried dispersion is present in an amount of about 20% to about 90% w/w of the composition. In some embodiments, the spray-dried dispersion is present in an amount of about 40% to 80% w/w of the composition.

In some embodiments, the pharmaceutical excipients are selected from the group consisting of a filler, a lubricant, and combinations thereof. In some embodiments, the filler is selected from the group consisting of a binder, a diluent, a disintegrant, a glidant, a surfactant, and combinations thereof.

In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg.

In some embodiments, the pharmaceutical composition is formulated as a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film. In some embodiments, the pharmaceutical composition is in tablet form. In some embodiments, the pharmaceutical composition is in capsule form. In some embodiments, the pharmaceutical composition is coated.

In some embodiments, the spray-dried dispersion is formulated for oral administration and exhibits a positive food effect when administered orally. In some embodiments, the spray-dried dispersion has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10. In some embodiments, wherein the spray-dried dispersion has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10.

Also provided herein is a method for preparing a pharmaceutical composition, comprising combining the spray-dried dispersion of the present disclosure with one or more pharmaceutically acceptable excipients.

Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective

amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure.

Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

In some embodiments, the spray-dried dispersion or the pharmaceutical composition is administered to the subject in a fed state. In some embodiments, the spray-dried dispersion or the pharmaceutical composition is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than 30%. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the spray-dried dispersion or the pharmaceutical composition.

In some embodiments, administering the spray-dried dispersion or the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof when comparing oral administration of the spray-dried dispersion or pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 10 to about 20. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 10 to about 20.

In some embodiments of the disclosed methods, the subject is a pediatric subject.

Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in therapy, for example, for use in any of the methods disclosed herein.

Also provided herein is use of a spray-dried dispersion of the present disclosure for manufacture of a medicament for use in any of the methods disclosed herein.

Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Also provided herein is a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

Also provided herein is use of pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

Also provided herein is pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy, for example, for use in any of the methods disclosed herein.

Also provided herein is use of pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods disclosed herein.

Also provided herein is a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, comprising orally administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of improving gastrointestinal absorption of

a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

In some embodiments, the subject is a pediatric subject.

Also provided herein is a method of improving oral bioavailability of a compound of Formula (I) in a subject, comprising orally administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in a method of improving oral bioavailability of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of improving oral bioavailability of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

In some embodiments, the subject is a pediatric subject.

Also provided herein is a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

Also provided herein is a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt, for use in therapy, for example, for use in any of the methods disclosed herein.

Also provided herein is use of a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt, for manufacture of a medicament for use in any of the methods disclosed herein.

Other features and advantages of the methods, processes, formulations, and uses provided herein will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 shows the dissolution performance of several spray-dried dispersion formulations in 0.5 wt% simulated intestinal fluid (SIF) in phosphate buffered saline (PBS), pH 6.5.

FIG. 2 shows the vertical membrane flux cell integrated in the μDiss Profiler™ used for the membrane flux assay.

FIG. 3 shows non-sink dissolution data for several spray-dried dispersion formulations and the compound of Formula (I) in 0.5 wt% SIF in PBS, pH 6.5.

FIG. 4 is a graph showing membrane flux of 1 mg/mL GB/IB 0.5 wt% SIF doses of the compound of Formula (I) and various spray-dried dispersion formulations over time. The solid lines indicate flux ($\mu g\ min^{-1}\ cm^{-2}$) and the broken lines indicate concentration (μg/mL) in 0.5% SIF.

FIG. 5 is a flow diagram of the spray drying manufacturing process used to prepare a 1000 g batch of a SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64.

FIGS. 6A and 6B are line graphs showing the pharmacokinetic results of a bioavailability and food effect study in dogs. FIG. 6A shows the results from Cohort 1 and FIG. 6B shows the results from Cohort 2.

FIG. 7 is a flow chart showing the study design of a Phase 1 study of the pharmacokinetics and food effect of the compound of Formula (I) in healthy adult subjects.

FIGS. 8A and 8B are line graphs showing the mean plasma concentration versus time profiles for the compound of Formula (I) under fasted and fed conditions, respectively, in healthy adult subjects.

FIGS. 9A-9C are spaghetti plots of the pharmacokinetics of the compound of Formula (I) in healthy adult subjects under fasted and fed conditions. FIG. 9A shows the $AUC_{0\text{-tlast}}$ values. FIG. 9B shows the $AUC_{0\text{-}\infty}$ values. FIG. 9C shows the C_{max} values.

FIG. 10 is a flow chart showing the study design of a Phase 1 study of the bioavailability, pharmacokinetics and food effect of the compound of Formula (I) in healthy adult subjects.

FIG. 11 shows the study design of a Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia.

FIGs. 12A and 12B show the arithmetic mean values for adrenocorticotropic hormone (ACTH) (FIG. 12A) and 17-hydroxyprogesterone (17-OHP) (FIG. 12B) for all 8 Cohort 1 subjects plotted at each time point for pre-treatment baseline (circles), day 1 (squares), and day 14 (triangles).

FIGs. 13A and 13B show arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for pre-treatment baseline (circles), day 1 (squares), and day 14 (triangles).

FIGs. 14A and 14B show the reduction of ACTH at timepoints 8-, 10-, and 12-hours postdose. FIG 14A shows the values for each time point as compared to baseline. FIG. 14B shows the mean values across all three timepoints.

FIGs. 15A and 15B show the reduction of 17-OHP at timepoints 8-, 10-, and 12-hours postdose. FIG 15A shows the values for each time point as compared to baseline. FIG. 15B shows the mean values across all three timepoints.

FIGs. 16A and 16B show the reduction of androstenedione at timepoints 8-, 10-, and 12-hours postdose. FIG 16A shows the values for each time point as compared to baseline. FIG. 16B shows the mean values across all three timepoints.

FIG. 17A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 17B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 17C: shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 18A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard

error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 18B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 18C shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 19A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 19B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 19C shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 20 is a scheme showing the manufacturing process for forming 50 mg capsules of the compound of Formula (I).

FIG. 21 is an alternative scheme showing the manufacturing process for forming 50 mg capsules of the compound of Formula (I).

FIGs. 22A and 22B show a scheme showing the manufacturing process for forming SDD granules of the compound of Formula (I).

FIG. 23 is a scheme showing the manufacturing process for forming 50 mg/nL liquid formulation 1 of the compound of Formula (I).

FIG. 24 is a scheme showing the manufacturing process for forming 50 mg/nL liquid formulation 2 of the compound of Formula (I).

FIG. 25 is an XRPD spectrum of the compound of Formula (I) free base crystalline form I.

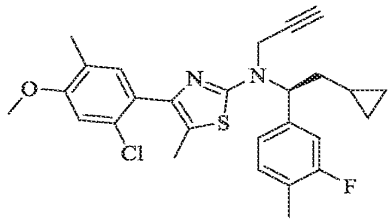
FIG. 26 is a DSC spectrum of the compound of Formula (I) free base crystalline form I.

FIG. 27 is an XRPD spectrum of the compound of Formula (I) tosylate crystalline form 1.

FIG. 28 is a DSC and TGA spectrum of the compound of Formula (I) tosylate crystalline form 1.

DETAILED DESCRIPTION

As described herein, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, is a selective CRF1 receptor antagonist that has been found to be effective treating congenital adrenal hyperplasia. Specifically, the compound of Formula (I) has been found to effectively reduce several biomarkers associated with congenital adrenal hyperplasia.

Newborn screening for CAH is performed by immunoassay to measure 17-OHP levels in heel-stick capillary blood specimens obtained within the first 72 hours of life. The blood sample is analyzed for 17-OHP by commercially available dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA; PerkinElmer, Waltham Massachusetts) (White et al., *J. Pediatr.* 163:10-12 (2013)). Second-tier screening tests utilizing biochemical and molecular genetic testing methods, performed between 8 and 14 days of life, are employed by nine states in the United States and strongly recommended by an additional 5 states. The biochemical method includes immunoassay with organic solvent extraction or liquid chromatography followed by tandem mass spectrometry to measure steroid ratios of 17-OHP, androstenedione, and 21-deoxycortisol to cortisol (*see, e.g.,* Speiser et al., *Int. J. Pediatr. Endocrinol.* 2010:494173,

2010). The genetic screen looks for *CYP21A2* mutations that are associated with CAH. While not widely employed in the U.S., the addition of a second screening could potentially improve the sensitivity of the overall screening process, where sensitivity of the first screen alone is approximately 72%.

In absence of results from the newborn screening, female infants with classical CAH are typically identified due to the presence of ambiguous genitalia. Males have normal genitalia at birth and therefore are not diagnosed unless newborn screening is conducted or other medical complications come to attention. Infants who are not initially diagnosed with CAH and suffer from the salt-wasting form of the disease are later diagnosed in the setting of poor weight gain, vomiting, hyperkalemia and hyponatremia within the first few weeks of life.

Treatment of CAH is based on normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment include cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women and to inhibit testicular adrenal rest tumors in men. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

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.,* Finkielstain 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 required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients (*see, e.g.,* Elnecave et al., *J. Pediatr. Endocrinol. Metab.* 21:1155-62 (2008); King et al., *J. Clin. Endocrinol. Metab.* 91(3):8656-59 (2006); Migeon et al., *Endocrinol. Metab. Clin. North Am.* 30:193-206 (2001)). Recently, best practices for the clinical management of congenital adrenal hyperplasia were published in the *Journal of Clinical Endocrinology and Metabolism* (Speiser, P.W., et al. *J. Clin. Endocrinol. Metab.* November 2018, 103(11): 1-46). This article is incorporated by reference in its entirety.

Corticotropin-releasing factor (CRF) was isolated from ovine hypothalami and identified as a 41-amino acid peptide. CRF has been found to produce profound alterations in endocrine, nervous, and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotropic hormone ("ACTH"), ß-endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (*see, e.g.,* Vale et al., *Science 213*:1394-1397, 1981). Secretion of CRF causes release of ACTH from corticotrophs in the anterior pituitary via binding to the CRF_1 receptor, a member of the class B family of G-protein coupled receptors.

Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF_1 receptor binding activity and which are capable of antagonizing the CRF_1 receptor remains a desirable goal and has been the subject of ongoing research and development for the treatment of anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse.

The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21-hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-hydroxyprogesterone (17-OHP). Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone causing virilization in females. In addition, 21-hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically cortisol and aldosterone. Cortisol is a critical negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

Definitions

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

The term "about" preceding a value for DSC, TGA, or T_g, which are reported as degrees Celsius, have an allowable variability of ±5°C. In all other instances, unless otherwise specified, the term "about" preceding a stated value includes the stated value and also includes ±20% of the stated value, and includes more specifically values of ±10%, ±5%, ±2%, and ±1% of the stated value.

To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that when a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any range therein.

"Room temperature" or "RT" refers to the ambient temperature of a typical laboratory, which is typically around 25°C.

"Spray-drying" refers to the method of producing a dry powder from a solution or slurry. The solution or slurry is atomized or rapidly dried with a hot gas, e.g., air or nitrogen, that causes the solvent to evaporate quickly and uniformly. A "spray-dried dispersion" refers to the powder obtained from the spray-drying process.

The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, co-solvents, complexing agents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, which are not biologically or otherwise undesirable. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic formulations is contemplated. Supplementary active ingredients can also be incorporated into the formulations. In addition, various excipients, such as are commonly used in the art, can be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman *et al.* (Eds.) (2010); *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, 12th Ed., The McGraw-Hill Companies.

"Subject," as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate. In some embodiments, the subject is a human.

In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having congenital adrenal hyperplasia (CAH). In some embodiments, the subject is suspected of having CAH. In some embodiments, the subject has a clinical record indicating that the subject has CAH (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein). In some embodiments, the subject is a pediatric subject.

The term "pediatric subject" as used herein refers to a subject under the age of 21 years at the time of diagnosis or treatment. The term "pediatric" can be further divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman et al., *Textbook of Pediatrics*, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph et al., *Rudolph's Pediatrics*, 21st Ed. New York: McGraw-Hill, 2002; and Avery et al., *Pediatric Medicine*, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

As used herein, the terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

The term "preventing," as used herein, means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

The term "administration" or "administering" refers to a method of giving a dosage of a compound or pharmaceutical formulation to a vertebrate or invertebrate, including a mammal, a bird, a fish, or an amphibian. The preferred method of administration can vary

depending on various factors, e.g., the components of the pharmaceutical formulation, the site of the disease, and the severity of the disease.

As used herein, "therapeutically effective amount" is an amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or an amount of a pharmaceutical composition comprising the compound of Formula (I), which is sufficient to achieve the desired effect and can vary according to the nature and severity of the disease condition, and the potency of the compound. A therapeutic effect is the relief, to some extent, of one or more of the symptoms of the disease, and can include curing a disease. "Curing" means that the symptoms of active disease are eliminated. However, certain long-term or permanent effects of the disease can exist even after a cure is obtained (such as, e.g., extensive tissue damage).

The term "amorphous" means a solid in a solid state that is a non-crystalline state. Amorphous solids are disordered arrangements of molecules and therefore possess no distinguishable crystal lattice or unit cell and consequently have no definable long range ordering. The solid state form of a solid may be determined by polarized light microscopy, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), or other standard techniques known to those of skill in the art.

As used herein, "time of day window" refers to a period of time defined by a window start time and a window stop time. These times all refer to local times where a sample was taken. The phrase "same time of day window" when referring to samples taken from the subject mean, e.g., that a sample taken at 8:15 a.m. and a sample taken at 9:15 a.m. are considered to be taken in the same time of day window of, e.g., 2 a.m. to 10 a.m. or 6 a.m. to 10 a.m.

Methods

The present disclosure relates to methods of treating congenital adrenal hyperplasia (CAH). The methods include administering to a subject a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a subject a therapeutically effective amount of a SDD of the present disclosure that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a subject a therapeutically effective amount of pharmaceutical composition of the present disclosure that contains a SDD that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Provided herein is a method of treating congenital adrenal hyperplasia (CAH) comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof to normalize or partially normalize levels of biomarkers associated with congenital adrenal hyperplasia. In some embodiments, normalizing or partially normalizing levels of biomarkers comprises reducing levels of elevated biomarkers or increasing levels of depressed biomarkers as compared to subject without CAH.

Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers associated with congenital adrenal hyperplasia. In some embodiments, the biomarkers are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

In some embodiments, the reduction in level of any of the biomarkers (e.g., any of 17-OHP, ACTH, and androstenedione) is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof. A day prior to administering the compound of Formula (I) applies to a subject that has not previously been administered the compound of Formula (I) within at least the past 24 hours.

In some embodiments, the circadian release of biomarkers associated with CAH occurs between the hours of 2 a.m. and 10 a.m. In other embodiments, the circadian release of biomarkers associated with CAH occurs between the hours of 6 a.m. and 10 a.m.

In some embodiments of any of the methods disclosed herein, the compound of Formula (I), or a pharmaceutically acceptable salt, is administered to the subject at nighttime or administration prior to sleep (i.e., bedtime administration). In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered six to eight hours prior to the circadian release of the biomarker. Administration prior to the circadian release may be adapted for shift workers (*e.g.*, those who work at night and sleep during the day), in which case administration will not necessarily occur at nighttime. Administration is

therefore dependent upon the expected circadian release of the biomarker, and can vary depending upon the individual's (*i.e.,* subject, patient) particular work and sleep patterns.

In some embodiments of the methods provided herein, the level of 17-hydroxyprogesterone is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25%. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50%. In some embodiments of the methods provided herein, the level of 17-hydroxyprogesterone is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

In some embodiments, the level of 17-hydroxyprogesterone is reduced to a level within the range of 17-hydroxyprogesterone expected for a subject without CAH, i.e., less than 1,000 ng/dL or less than 200 ng/dL.

In some embodiments of the methods provided herein, the level of adrenocorticotropic hormone is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50%.

In some embodiments of the methods provided herein, the level of adrenocorticotropic hormone is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

In some embodiments, the level of adrenocorticotropic hormone is reduced to a level within the range of adrenocorticotropic hormone expected for a subject without CAH.

In some embodiments of the methods provided herein, the level of androstenedione is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments,

the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

In some embodiments of the methods provided herein, the level of androstenedione is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

In some embodiments, the level of androstenedione is reduced to a level within the range of androstenedione expected for a subject without CAH, i.e., less than 200 ng/dL.

Also provided herein is a method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce one or more biomarker of CAH in a subject, e.g. reduce the androstenedione in the subject. Growth impairment can refer to, e.g., accelerated height velocity, accelerated weight velocity, and/or accelerated bone age.

Provided herein is a method for reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

Provided herein is a method for reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the corticosteroid is a glucocorticoid.

Also provided herein is a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. The long-term effects of glucocorticoid treatment are well documented in the art (see, e.g., Oray, M. et al. (2016): Long-term effect of glucocorticoids, *Expert Opinion on Drug Safety*. DOI: 10.1517/14740338.2016.1140743). Such side effects are associated with every biological system, e.g., musculoskeletal (e.g., osteoporosis, avascular necrosis of bone, and

myopathy), endocrine and metabolic (e.g., hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression), gastrointestinal (e.g., gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis), cardiovascular (e.g., hypertension, coronary heart disease, ischemic heart disease, heart failure), dermatologic (e.g., dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, and hair loss), neuropsychiatric (e.g., mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, and delirium), ophthalmologic (e.g., cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, and central serous chorioretinopathy), and immunologic (e.g., suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections).

Accordingly, in some embodiments, the side effects of glucocorticoid treatment are selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, reactivation of latent infections, and any combination thereof.

Provided herein is a method of treating congenital adrenal hyperplasia in a subject comprising

(i)measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii)analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii)administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

In some embodiments, the method further comprises (iv) measuring the level of the one or more biomarkers after administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i). In some embodiments, the method further comprises (v) continuing the administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

In some embodiments, steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

In some embodiments, steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

In some embodiments, step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

In some embodiments, step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

In some embodiments of the methods of the present disclosure, the compound of Formula (I) is administered at an amount equivalent to from about 25 mg to about 150 mg of the compound of Formula (I) free base. In some embodiments, compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at an amount equivalent to about 50 mg or about 100 mg of the compound of Formula (I) free base.

In some embodiments of the methods disclosed herein, compound of Formula (I) is administered in the free base form.

In some embodiments of the methods disclosed herein, the compound of Formula (I) is administered once daily.

Also provided herein is a method of treating CAH in a pediatric subject. The methods include administering to a pediatric subject a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a pediatric subject a therapeutically effective amount of a SDD of the present disclosure that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a pediatric subject a therapeutically effective amount of pharmaceutical composition of the present disclosure that contains a SDD that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pediatric subject is a neonate. In some embodiments, the pediatric subject is an infant. In some embodiments, the pediatric subject is a child. In some embodiments, the pediatric subject is an adolescent.

In some embodiments of the methods of the present disclosure, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject in a fed state. The term "fed state," as used herein, refers to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof from about 1 hour before consumption of food or a nutritional composition to about 1 hour after consumption of food or a nutritional composition. The term "fasted state," as used herein, refers to a gap of at least two hours between consumption of food or a nutritional composition and administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject with food or a nutritional composition, such as a nutritional supplement or formula, a meal replacement beverage, a liquid dietary supplement, or a high caloric liquid meal. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject within about 1 hour before the subject has consumed food or a nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject within about 1 hour after the subject has consumed food or a nutritional composition. Examples of suitable nutritional compositions include, but are not limited to, infant formulas, dietary supplements, dietary substitutes, and rehydration compositions. In some embodiments, the food is a product containing concentrated calories and protein. In some embodiments, the nutritional composition is a composition utilized for enteral and parenteral supplementation for infants, specialty infant formulas, supplements for the elderly, and supplements for those with

gastrointestinal difficulties and/or malabsorption. Adult and pediatric nutritional formulas are well known in the art and are commercially available (e.g., Similac®, Ensure®, Jevity® and Alimentum® from Ross Products Division, Abbott Laboratories, Columbus, Ohio).

In some embodiments, the nutritional composition is in liquid form. The energy density of the nutritional compositions, when in liquid form, can range from about 0.6 Kcal to about 3 Kcal per mL. In some embodiments, the nutritional composition is in solid or powdered form. When in solid or powdered form, the nutritional supplements can contain from about 1.2 to more than 9 Kcals per gram, such as about 3 to 7 Kcals per gram.

In some embodiments, the nutritional composition is a meal replacement bar. Examples include PowerBar®, Glucerna® bars, Choice DM® bars, Ensure® bars, and Boost® bars. In some embodiments, the nutritional composition is a nutrition shake or meal replacement beverage. Commercially available examples include the Ensure® branded adult products (such as Ensure® Original, Ensure® Plus, Ensure® Enlive, Ensure® High Protein, Ensure® Clear, and Ensure® Light), Glucerna®, Choice DM®, Slim Fast®, Pediasure®, Glytrol®, and Resource®. In some embodiments, the nutritional composition is Ensure® Plus. In some embodiments, the nutritional composition is vanilla-flavored Ensure® Plus. Ensure Plus® is a high calorie liquid dietary supplement that contains 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

In some embodiments of the methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject before administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject at the same time as administration of the nutritional composition.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject, followed by administration of the nutritional composition. In some embodiments, the nutritional composition is administered about 1 minute, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, or about 60

minutes, or within a range defined by any of the preceding values after administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the nutritional composition is administered 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, or 60 minutes, or within a range defined by any of the preceding values after administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the nutritional composition is administered within 30 minutes of administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

In some embodiments, the nutritional composition is administered to the subject, followed by administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered about 1 minute, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, or about 60 minutes, or within a range defined by any of the preceding values after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, or 60 minutes, or within a range defined by any of the preceding values after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered within 30 minutes of administering the nutritional composition. In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

In some embodiments of the methods, a food effect is observed between administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof in a fed state versus a fasted state. The term "food effect," as used herein, refers to the relative difference in AUC (area under the curve $AUC_{(0-t)}$ and/or $AUC_{(0-\infty)}$) or C_{max} (maximum plasma concentration or peak plasma concentration) of an active substance, when the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally to a subject, concomitantly with

food or in a fed state as compared to the same values when the same compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered in a fasted state. The food effect (F) is calculated as:

$$F\% = [(X_{fasted} - X_{fed}) / X_{fasted}] \times 100$$

where X_{fed} and X_{fasted} are the values of AUC ($AUC_{(0-t)}$ and/or $AUC_{(0-\infty)}$) or C_{max} in the fed and fasted state, respectively. In some embodiments, an increased, or positive, food effect is observed when the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to a subject in a fed state. In some embodiments, administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in an increased, or positive, food effect, whereby an increased C_{max} and/or AUC are observed when administered orally in the fed state as compared to the fasting state.

In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10, such as about 5 to about 9, about 5 to about 8, about 5 to about 7, about 5 to about 6, about 6 to about 10, about 6 to about 9, about 6 to about 8, about 6 to about 7, about 7 to about 10, about 7 to about 9, about 7 to about 8, about 8 to about 10, about 8 to about 9, or about 8 to about 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5, about 6, about 7, about 8, about 9, or about 10, or within a range defined by any of the preceding values. In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is about 10 to about 20.

In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is 5 to 10, such as 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 10, 6 to 9, 6 to 8, 6 to 7, 7 to 10, 7 to 9, 7 to 8, 8 to 10, 8 to 9, or 8 to 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is 5, 6, 7, 8, 9, or 10, or within a range defined by any of the preceding values.

In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10, such as about 5 to about 9, about 5 to about 8, about 5 to about 7, about 5 to about 6, about 6 to about 10, about 6 to about 9, about 6 to about 8, about 6 to about 7, about 7 to about 10, about 7 to about 9, about 7 to about 8, about 8 to about 10, about 8 to about 9, or about 8 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5, about 6, about 7, about 8, about 9, or about 10, or within a range defined by any of the preceding values. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is about 1.5

to about 3 times higher in the fed stated compared to the fasted state. In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is 5 to 10, such as 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 10, 6 to 9, 6 to 8, 6 to 7, 7 to 10, 7 to 9, 7 to 8, 8 to 10, 8 to 9, or 8 to 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is 5, 6, 7, 8, 9, or 10, or within a range defined by any of the preceding values. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is 1.5 to 3 times higher in the fed stated compared to the fasted state. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is about 2 times higher in the fed stated compared to the fasted state. In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 10 to about 20.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a meal. In some embodiments, the meal is a high fat, high caloric meal. In some embodiments, the meal is a low fat, low caloric meal. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered within approximately 5 minutes after the start of the meal. In some embodiments, the meal is an evening meal. In some embodiments, the meal is a morning meal.

In some embodiments, the fed state is with a high fat meal. In some embodiments, the fed state is with a low fat meal. The FDA has provided draft guidelines regarding high fat and low fat meals ("Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations Guidance for Industry," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), February 2019, Clinical Pharmacology). Table 1 shows test meal definitions provided by the FDA guidance.

Table 1

Meal Type	Total Kcal	Fat		
		Kcal	Grams	Percent
High-Fat	800-1000	500-600	55-65	50
Low-Fat	400-500	100-125	11-14	25

The composition of a high fat meal provided by the FDA guidance is depicted in Table 2.

Table 2. Composition of a High Fat Meal*

Total Calories	800-1000
Calories from Protein	150
Calories from Carbohydrates	250
Calories from Fat	500-600
An Example of a High Fat Breakfast	• Two eggs fried in butter • Two strips of bacon • Two slices of toast with butter • Four ounces of hash brown potatoes • Eight ounces of whole milk

*50 percent of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained.

The composition of a low fat meal provided by the FDA guidance is depicted in Table 3.

Table 3. Composition of a Low Fat Meal

Total Calories	400-500
Fat (g)	250
Percent Calories from Fat	25
An Example of a Low Fat Breakfast*	• Eight ounces milk (1 percent fat) • One boiled egg • One packet flavored instant oatmeal made with water

*This low-fat breakfast contains 387 calories and has 10 grams of fat.

In some embodiments, a high fat meal contains 800-1000 total Kcal and 500-600 fat Kcal. In some embodiments, a low fat meal contains 400-500 total Kcal and 100-125 fat Kcal.

Also provided herein is a method of improving gastrointestinal absorption of a compound of Formula (I), or pharmaceutically acceptable salt thereof, in a subject. The method includes orally administering to the subject a pharmaceutical composition of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I), or pharmaceutically acceptable salt thereof, which has not been prepared as a spray-dried dispersion. In some embodiments, the subject is a pediatric subject.

Also provided herein is a method of improving oral bioavailability of a compound of Formula (I), or pharmaceutically acceptable salt thereof, in a subject. The method includes orally administering to the subject a pharmaceutical composition of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I), or pharmaceutically acceptable salt thereof, which has not been prepared as a spray-dried dispersion.

In some embodiments of the methods provided herein, the subject is a pediatric subject.

Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition is a lipidic semi-solid formulation. In some embodiments, the pharmaceutical composition is a liquid formulation. In some embodiments, the pharmaceutical composition is administered to the subject in a fed state.

Also provided herein is a pharmaceutical composition of the present disclosure for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject. In some embodiments, the subject is in a fed state.

In some embodiments, the pharmaceutical composition is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

In some embodiments, the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is

1.5 to 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1.5 to 3.

In some embodiments, the subject is a pediatric subject.

In some embodiments, the pharmaceutical composition is formulated for oral administration and exhibits a positive food effect when administered orally. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 10 to about 20. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 10 to about 20. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1 to about 4 or about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1 to about 4. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1.5 to about 3. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1 to 4 or 5 to 10. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of 1 to 4 or 5 to 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1 to 4. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of 1 to 4. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1.5 to 3. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of 1.5 to 3.

In some embodiments, the pharmaceutical composition is administered to the subject with a meal. In some embodiments, the meal is a high fat meal. In some embodiments, the meal is a low fat meal. In some embodiments, the pharmaceutical composition is administered

within about 5 minutes after the start of the meal. In some embodiments, the meal is an evening meal. In some embodiments, the meal is a morning meal.

In some embodiments, administering the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof of the compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the AUC of the compound

of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1.5 to 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1.5 to 3.

For the avoidance of doubt, also provided herein is the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, or corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the corresponding methods, as described herein.

For the avoidance of doubt, also provided herein is use of the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

For the avoidance of doubt, also provided herein is use of the corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

Reduction in glucocorticoid burden, adrenal androgens and precursors

Glucocorticoids are a class of corticosteroids, which are a class of steroid hormones. Glucocorticoids are corticosteroids that bind to the glucocorticoid receptor that is present in almost every vertebrate animal cell. In some embodiments, the subject is concurrently receiving a dose of a glucocorticoid. In some embodiments, the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate. In some embodiments, the glucocorticoid is cortisol (hydrocortisone). In some embodiments, the glucocorticoid is cortisone. In some embodiments, the glucocorticoid is prednisone. In some embodiments, the glucocorticoid is dexamethasone.

In some embodiments, the glucocorticoid dose is measured in hydrocortisone equivalents. In some embodiments, the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents. Any glucocorticoid can be given in a dose that provides approximately the same glucocorticoid effects as normal cortisol production; this is referred to as physiologic, replacement, or maintenance dosing.

In some embodiments, the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically

acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m^2/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m^2/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m^2/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the glucocorticoid dose concurrently given to the subject is a normal physiological dose of hydrocortisone equivalents. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 2 to about 16 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 4 to about 12 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 5 to about 11 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 6 to about 10 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 7 to about 9 mg/m^2/day. In

some embodiments, a normal physiological dose of hydrocortisone equivalents is about 4 to about 9 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 8 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 12 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is less than about 8 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15 or about 16 mg/m^2/day, or within a range defined by any of the preceding values.

In some embodiments, the glucocorticoid dose concurrently given to the subject is at the upper limit of normal of a normal physiological dose of hydrocortisone equivalents. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the upper limit of normal is 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 2 times the normal physiological dose. In some embodiments, the upper limit of normal is about 2.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, or about 3.0 times the normal physiological dose, or within a range defined by any of the preceding values.

In some embodiments, the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the

glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period

of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof,

wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the glucocorticoid dose of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction

of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of 17-hydroxyprogesterone of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40%

after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is less than about 1.5 times the upper limit of normal after a time

period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of adrenocorticotropic hormone of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the level of androstenedione is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt

thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of androstenedione of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the level of testosterone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of testosterone of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than 1.5 times the upper limit of normal and the level of androstenedione is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal

limits and the level of androstenedione is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of 17-hydroxyprogesterone and androstenedione of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition comprising the compound of

Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the quality of life as measured by the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) in the subject is improved after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) is relative to the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) results prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, fatigue is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in fatigue is relative to the fatigue prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, sleep is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in sleep is relative to the sleep prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, insulin resistance is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of insulin resistance is relative to the insulin resistance prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, glucose tolerance is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof,

wherein the reduction in glucose tolerance is relative to the glucose tolerance prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, glucose control is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in glucose control is relative to the glucose control prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, lipid levels reflecting dyslipidemia are reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in lipid levels is relative to the lipid levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, lipid levels reflecting hyperlipidemia are reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in lipid levels is relative to the lipid levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, bone mineral density is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in bone mineral density is relative to the bone mineral density prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, bone turnover is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in bone turnover is relative to the bone turnover prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, fat mass is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in fat mass is relative to the fat mass prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, body weight is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in body weight is relative to the body weight prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, central obesity is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof,

wherein the decrease in central obesity is relative to the central obesity prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, blood pressure is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in blood pressure is relative to the blood pressure prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the severity of hirsutism is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in the severity of hirsutism is relative to the severity of hirsutism prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, menstrual cyclicity is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in menstrual cyclicity is relative to the menstrual cyclicity prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, control of testicular adrenal rest tumor is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in control of testicular adrenal rest tumor is relative to the control of testicular adrenal rest tumor prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, fertility is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in fertility is relative to the fertility prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, gonadotropin levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in gonadotropin levels is relative to the gonadotropin levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, progesterone levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in progesterone levels is relative to the progesterone levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, semen levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in semen levels is relative to the semen levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, LH (luteinizing hormone) levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in LH levels are relative to the LH levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the time period of administration is at least about 4 weeks. In some embodiments, the time period of administration is at least about 24 weeks. In some embodiments, the time period of administration is at least about one year. In some embodiments, the time period of administration is at least 4 weeks. In some embodiments, the time period of administration is at least 24 weeks. In some embodiments, the time period of administration is at least one year. In some embodiments, the time period of administration is less than about 1 day. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6 or 7 days, or within a range of any of the preceding values. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 weeks, or within a range of any of the preceding values. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, or within a range of any of the preceding values. It is understood that comparative measurements occur preferably during the morning.

In some embodiments, the subject is a pediatric subject. In some embodiments, the pediatric subject is less than or equal to six years old. In some embodiments, the pediatric subject is greater than six years old and less than eleven years old. In some embodiments, the pediatric subject is greater than ten years old and less than fifteen years old. In some embodiments, the pediatric subject is greater than fourteen years old and less than nineteen years old.

In some embodiments, the subject is an adult subject. In some embodiments, the subject is over eighteen years old. In some embodiments, the subject is female. In some embodiments, the subject is male.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described herein. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is

administered as a pharmaceutical composition described in Example 9. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 11. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 12. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 13. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid salt described herein.

For the avoidance of doubt, also provided herein is the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, or corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the corresponding methods, as described herein.

For the avoidance of doubt, also provided herein is use of the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

For the avoidance of doubt, also provided herein is use of the corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

p-Toluenesulfonic Acid Salt

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt thereof is 4-(2-chloro-4-methoxy -5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

In some embodiments, the 4-(2-chloro-4-methoxy -5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt is a crystalline salt. In some embodiments, the p-toluenesulfonic acid crystalline salt has Form 1.

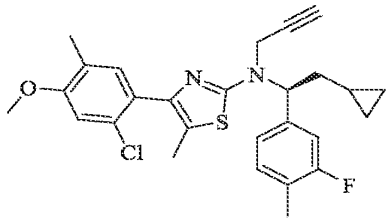
In some embodiments, the p-toluenesulfonic acid crystalline salt has an X-ray powder diffraction pattern as substantially shown in Figure 27. In some embodiments, the p-toluenesulfonic acid crystalline salt has a DSC thermogram substantially as depicted in Figure 28. In some embodiments, the p-toluenesulfonic acid crystalline salt has a thermogravimetric analysis (TGA) thermogram substantially as depicted in Figure 28.

In some embodiments, the p-toluenesulfonic acid crystalline salt has at least one X-ray powder diffraction (XRPD) peak, in terms of 2-theta (± 0.2 degrees), selected 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least two X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least three X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least four X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has characteristic X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), at 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has an endothermic peak having an onset of melt at about 156 °C (22.2 J/g) in a differential scanning calorimetry (DSC) thermogram.

Lipidic Semi-Solid Formulation

Provided herein is a lipidic semi-solid formulation, which is a pharmaceutical composition comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or within a range of any of the preceding values.

In some embodiments, the pharmaceutical composition comprises an oily phase vehicle. An oily phase vehicle is a solvent that is poorly miscible with water. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 50 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 20 wt% to about 50 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 35 wt% to about 45 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 39 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 wt% of the oily phase vehicle, or within a range of any of the preceding values.

In some embodiments, the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the oily phase vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides are Labrafac TM Lipophile WL1349. In some embodiments, the medium-chain triglycerides are Miglyol 812N.

In some embodiments, the pharmaceutical composition comprises an emulsifying agent. An emulsifying agent is a compound or substance that acts as a stabilizer for emulsions. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 50 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 10 wt% to about 30 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 15 wt% to about 25 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises

about 20 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 wt% of the emulsifying agent, or within a range of any of the preceding values.

In some embodiments, the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the emulsifying agent is propylene glycol dicaprylate/dicaprate. In some embodiments, the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

In some embodiments, the pharmaceutical composition comprises a nonionic surfactant. A nonionic surfactant is a substance with a hydrophilic head and a hydrophobic tail that has no charge that is a formulation component added to improve solubility or emulsion properties. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 50 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 10 wt% to about 30 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 15 wt% to about 25 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 19 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 wt% of the nonionic surfactant, or within a range of any of the preceding values.

In some embodiments, the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides. In some embodiments, the nonionic surfactant is lauroyl polyoxyl-32 glycerides. In some embodiments, the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.

In some embodiments, the pharmaceutical composition comprises a solubilizing agent. A solubilizing agent is a solvent that assists with solubilizing the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 50 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 20 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 15 wt% of the solubilizing agent. In some

embodiments, the pharmaceutical composition comprises about 11 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% of the solubilizing agent, or within a range of any of the preceding values.

In some embodiments, the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer. In some embodiments, the solubilizing agent is vitamin E polyethylene glycol succinate. In some embodiments, the vitamin E polyethylene glycol succinate is Kolliphor® TPGS. In some embodiments, the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.

In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) an oily phase vehicle;

(c) an emulsifying agent;

(d) a nonionic surfactant; and

(e) a solubilizing agent.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 35 wt% to about 45 wt% of an oily phase vehicle;

(c) about 15 wt% to about 25 wt% of an emulsifying agent;

(d) about 15 wt% to about 25 wt% of a nonionic surfactant; and

(e) about 5 wt% to about 15 wt% of a solubilizing agent.

In some embodiments, the pharmaceutical composition comprises:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 39 wt% of an oily phase vehicle;

(c) about 20 wt% of an emulsifying agent;

(d) about 19 wt% of a nonionic surfactant; and

(e) about 11 wt% of a solubilizing agent.

In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) a medium-chain triglycerides component;

(c) a propylene glycol dicaprylate/dicaprate component;

(d) a lauroyl polyoxyl-32 glycerides component; and

(e) a vitamin E polyethylene glycol succinate component.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) about 35 wt% to about 45 wt% of medium-chain triglycerides;

(c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;

(d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and

(e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.

In some embodiments, the pharmaceutical composition comprises:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) about 39 wt% of medium-chain triglycerides;

(c) about 20 wt% of propylene glycol dicaprylate/dicaprate;

(d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and

(e) about 11 wt% of vitamin E polyethylene glycol succinate.

In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 15 to about 40 centipoise at about 45 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 26 to about 30 centipoise at about 45 °C. In some embodiments, the lipidic semi-solid pharmaceutical

composition has a viscosity between about 5 to about 25 centipoise at about 60 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 14 to about 18 centipoise at about 60 °C.

In some embodiments, the pharmaceutical composition does not comprise a combination of mannitol, croscarmellose sodium, maize starch, hydroxypropyl methylcellulose, and magnesium stearate.

In some embodiments, the pharmaceutical composition does not comprise at least one of mannitol, croscarmellose sodium, maize starch, hydroxypropyl methylcellulose, and magnesium stearate.

In some embodiments, the pharmaceutical composition comprises a compound of Formula (I), or pharmaceutically acceptable salt thereof, in crystalline form. In some embodiments, the pharmaceutical composition comprises a compound of Formula (I), or pharmaceutically acceptable salt thereof, in amorphous form. In some embodiments, the pharmaceutical composition comprises a compound of Formula (I) as a free base. In some embodiments, the crystalline form of the compound of Formula (I) is of Form I.

In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 75 mg to about 150 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 100 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 25 mg, based on the weight of the free base.

In some embodiments, the pharmaceutical composition is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film. In some embodiments, the pharmaceutical composition is in tablet form. In some embodiments, the pharmaceutical composition is in capsule form. In some embodiments, the dosage form is coated.

Some embodiments provide a method for preparing the pharmaceutical composition, comprising:

(a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;

(b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and

(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

In some embodiments, the method further comprises:

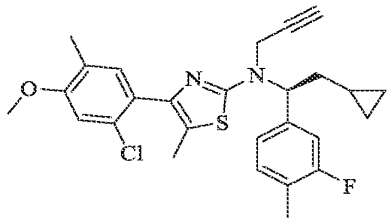
(d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and

(e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

Liquid Formulations

Provided herein is a pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

(b) one or more of a sweetener, an anti-oxidant, and a flavor; and

(c) a liquid vehicle.

In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free

base. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or within a range of any of the preceding values.

In some embodiments, the pharmaceutical composition comprises a sweetener. A sweetener is a formulation component added to improve taste. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 1.5 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.1 w/v% to about 0.5 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.15 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.2, 0.3, 0.4, or 0.5 w/v% of the sweetener, or within a range of any of the preceding values.

In some embodiments, the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and avantame. In some embodiments, the sweetener is saccharin.

In some embodiments, the pharmaceutical composition comprises an anti-oxidant. An anti-oxidant is a formulation component included to improve stability by preventing oxidation. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.17 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.2, 0.3, 0.4, or 0.5 w/v% of the anti-oxidant, or within a range of any of the preceding values.

In some embodiments, the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid. In some embodiments, the anti-oxidant is butylated hydroxytoluene.

In some embodiments, the pharmaceutical composition comprises a flavor. A flavor is a formulation component added to mask taste through aromatics. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 0.5 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.05 w/v% to about 0.2 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.10 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19 or 0.2 w/v% of the flavor, or within a range of any of the preceding values.

In some embodiments, the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetrarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor. In some embodiments, the flavor is FONA orange flavor.

A liquid vehicle is a solvent capable of dissolving or partially dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the purposes of delivery as an oral dosing solution. In some embodiments, the pharmaceutical composition comprises about 50 w/v% to about 99.9 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 90 w/v% to about 99 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 92 w/v% to about 97 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 94.6 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 w/v% of the liquid vehicle, or within a range of any of the preceding values.

In some embodiments, the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the liquid vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides is Labrafac Lipophile WL1349.

In some embodiments, the pharmaceutical composition further comprises a surfactant. A surfactant is a formulation component added to improve solubility or emulsion properties. In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 50 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 10 w/v% to about 30 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 20 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 w/v% of the surfactant, or within a range of any of the preceding values.

In some embodiments, the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters. In some

embodiments, the surfactant is oleoyl polyoxyl-6 glycerides. In some embodiments, the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

In some embodiments, the pharmaceutical composition comprises about 50 w/v% to about 90 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 70 w/v% to about 80 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 75 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 74.6 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 w/v% of the liquid vehicle, or within a range of any of the preceding values.

In some embodiments, the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the liquid vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides is Labrafac Lipophile WL1349.

In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) a sweetener;

(c) an anti-oxidant;

(d) a flavor; and

(e) a liquid vehicle.

In some embodiments, the pharmaceutical composition further comprises a surfactant.

In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;

(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;

(d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and

(e) about 92 w/v% to about 97 w/v% of a liquid vehicle.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of a sweetener;

(c) about 0.17 w/v% of an anti-oxidant;

(d) about 0.1 w/v% of a flavor; and

(e) about 94.6 w/v% of a liquid vehicle.

In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;

(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;

(d) about 0.05 w/v% to about 0.2 w/v% of a flavor;

(e) about 15 w/v% to about 25 w/v% of a surfactant; and

(f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of a sweetener;

(c) about 0.17 w/v% of an anti-oxidant;

(d) about 0.1 w/v% of a flavor;

(e) about 20 w/v% of a surfactant; and

(f) about 75 w/v% of a liquid vehicle.

In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) saccharin;

(c) butylated hydroxytoluene;

(d) FONA orange flavor; and

(e) medium-chain triglycerides.

In some embodiments, the pharmaceutical composition further comprises oleoyl polyoxyl-6 glycerides.

In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;

(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;

(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and

(e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of saccharin;

(c) about 0.17 w/v% of butylated hydroxytoluene;

(d) about 0.1 w/v% of FONA orange flavor; and

(e) about 94.6 w/v% of medium-chain triglycerides.

In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;

(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;

(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;

(e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and

(f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of saccharin;

(c) about 0.17 w/v% of butylated hydroxytoluene;

(d) about 0.1 w/v% of FONA orange flavor;

(e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and

(f) about 75 w/v% of medium-chain triglycerides.

In some embodiments, the pharmaceutical composition comprises the compound of Formula (I) as a free base.

In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 50 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 100 mg/mL, based on the weight of the free base.

In some embodiments, the liquid pharmaceutical composition has a viscosity between about 1 to about 50 centipoise at about 25 °C.

Some embodiments provide a method for preparing a pharmaceutical composition comprising:

(a) mixing a liquid vehicle with a sweetener;

(b) mixing the mixture of step (a) with an anti-oxidant and a flavor;

(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and

(d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

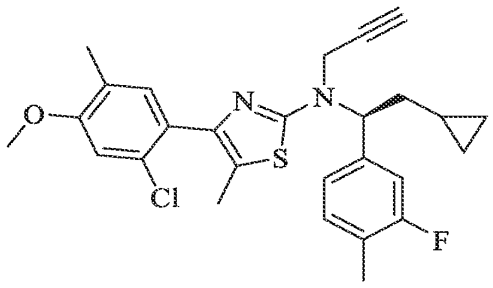
In some embodiments, step (a) of the method comprises mixing a liquid vehicle with a sweetener and a surfactant.

Spray-dried dispersions

The methods and uses of the present disclosure may comprise administering a spray-dried dispersion (SDDs) of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and to the use of the SDDs in the treatment of congenital adrenal hyperplasia (CAH).

In some embodiments, concentration and bioavailability enhancement in an aqueous environment of a low-solubility drug in a spray-dried dispersion is achieved if the SDD exhibits one or more properties, including, for example: (1) the solid dispersion is substantially homogeneous; (2) the drug is substantially amorphous; (3) the SDD has a relatively high drug loading; and (4) the SDD has a low residual solvent content. In some embodiments, the dispersion, when administered to an aqueous environment, provides at least a temporary dissolved drug concentration in the aqueous environment that is greater than the solubility of the crystalline form of the drug in the same environment. The aqueous environment can be, for example, an *in vitro* environment, such as a dissolution test media (e.g., phosphate buffered saline (PBS) solution), or an *in vivo* environment, such as the gastrointestinal (GI) tract of an animal, for example, a human. In some embodiments, the aqueous environment is the lower GI tract, such as the small intestine and large intestine.

Provided in the present disclosure is a spray-dried dispersion that contains a polymer and a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof. In some embodiments, the SDD includes a polymer selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from about 1:1 to about 1:9.

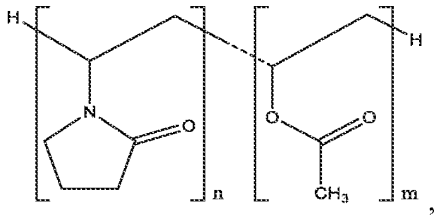
In some embodiments, the polymer is a neutral polymer. For example, the polymer does not contain any charged functional groups. In some embodiments, the neutral polymer is a cellulosic polymer. For example, the cellulosic polymer can be a polymer with at least one ester- and/or ether-linked substituent in which the polymer has a degree of substitution of at least 0.05 for each substituent. Examples of suitable neutral polymers include, but are not limited to, hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

In some embodiments, the polymer is an enteric polymer. An "enteric polymer," as used herein, is a polymeric substance that is substantially insoluble and/or substantially stable under acidic conditions exhibiting a pH of less than about 7 and which is substantially soluble or can decompose under conditions exhibiting a pH of about 7 or more. Examples of suitable enteric polymers include, but are not limited to, carboxymethyl ethyl cellulose (CMEC), cellulose acetate phthalate (CAP), cellulose acetate succinate (CAS), methylcellulose phthalate, hydroxymethyl ethyl cellulose phthalate, hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), polyvinyl alcohol phthalate, polyvinyl butyrate phthalate, polyvinyl acetal phthalate, a copolymer of vinyl acetate/maleic anhydride, a copolymer of vinylbutylether/maleic anhydride, a copolymer of styrene/maleic acid monoester, a copolymer of methyl acrylate/methacrylic acid, a copolymer of styrene/acrylic acid, a copolymer of methyl acrylate/methacrylic acid/octyl acrylate, a copolymer of methacrylic acid/methyl methacrylate, an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, a methacrylic copolymer, and mixtures thereof. In some embodiments, the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl

cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer. In some embodiments, the enteric polymer is a Eudragit® polymer sold by Evonik Industries (Essen, Germany). In some embodiments, the enteric polymer is an amino methacrylate copolymer. In some embodiments, the amino methacrylate copolymer is Eudragit® E PO/100. In some embodiments, the enteric polymer is an ammonioalkyl methacrylate copolymer. In some embodiments, the ammonioalkyl methacrylate copolymer is Eudragit® RLPO. In some embodiments, the enteric polymer is a methacrylic copolymer. In some embodiments, the methacrylic copolymer is Eudragit® L100 or Eudragit® S100.

In some embodiments, the polymer is a pyrrolidone polymer. For example, the pyrrolidone polymer can be a vinyl pyrrolidone polymer, such as polyvinyl pyrrolidone (PVP) or polyvinyl pyrrolidone vinyl acetate (PVP/VA), including homopolymers and copolymers of PVP and homopolymers and copolymers of N-vinyl pyrrolidone. In some embodiments, the pyrrolidone polymer is PVP/VA. In some embodiments, the PVP/VA is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 30:70 to about 70:30 by weight, such as about 40:60 to about 60:40 by weight, or about 45:55 to about 55:45 by weight. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 30:70, about 35:65, about 40:60, about 45:55, about 50:50, about 55:45, about 60:40, about 65:35, or about 70:30 by weight. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight.

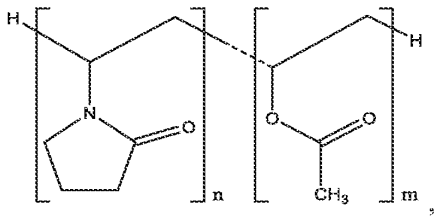
In some embodiments, the pyrrolidone polymer has the structure:



,

where the value of n is about 1 to about 2 times the value of m. For example, the value of n can be about 1, about 1.05, about 1.1, about 1.15, about 1.16, about 1.2, about 1.25, about 1.3, about 1.35, about 1.4, about 1.45, about 1.5, about 1.55, about 1.6, about 1.65, about 1.7, about 1.75, about 1.8, about 1.85, about 1.9, about 1.95, or about 2 times the value of m, or a value within a range defined by any of the preceding values. In some embodiments, the value of n is about 1.16 times the value of m. In some embodiments, the copolymer is copovidone, and the value of n is about 1.16 times the value of m.

In some embodiments, the pyrrolidone polymer has the structure:



where the value of n is 1 to 2 times the value of m. For example, the value of n can be 1, 1.05, 1.1, 1.15, 1.16, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, or 2 times the value of m, or a value within a range defined by any of the preceding values. In some embodiments, the value of n is 1.16 times the value of m. In some embodiments, the copolymer is copovidone, and the value of n is 1.16 times the value of m.

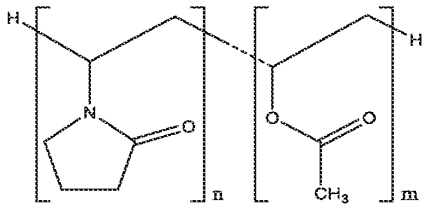
In some embodiments, the polymer used in the disclosed SDDs is present in an amount sufficient to increase the maximum drug concentration of the amorphous form of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the environment of use (e.g., aqueous environment) relative to a control composition that contains an equivalent amount of a crystalline form of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, but without polymer. In some embodiments, once the SDD is introduced into an environment of use (e.g., aqueous environment), the polymer increases the aqueous concentration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, relative to the control composition. It is to be understood that the control composition is free from solubilizers or other components that would materially affect the solubility of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is in solid form in the control composition.

In some embodiments of the SDDs, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from about 1:1 to about 1:9. For example, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer can be about 1:1 to about 1:8, about 1:1 to about 1:7, about 1:1 to about 1:6, about 1:1 to about 1:5, about 1:1 to about 1:4, about 1:1 to about 1:3, about 1:1 to about 1:2, about 1:1 to about 1:1.5, about 1:1.5 to about 1:9, or about 1:2.5 to about 1:4. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:9, about 1:8, about 1:7.5, about 1:7, about 1:6, about 1:5, about 1:4, about 1:3, about 1:2.5, about 1:2, about 1:1.5, or about 1:1, or a weight ratio within a range defined by any of the preceding values. In some embodiments, the weight

ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:9. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:1.5. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:1.

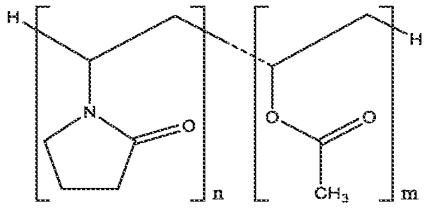
In some embodiments of the SDDs, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from 1:1 to 1:9. For example, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer can be 1:1 to 1:8, 1:1 to 1:7, 1:1 to 1:6, 1:1 to 1:5, 1:1 to 1:4, 1:1 to 1:3, 1:1 to 1:2, 1:1 to 1:1.5, 1:1.5 to 1:9, or 1:2.5 to 1:4. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:9, 1:8, 1:7.5, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2.5, 1:2, 1:1.5, or 1:1, or a weight ratio within a range defined by any of the preceding values. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:9. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:1.5. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:1.

In some embodiments, the spray dried dispersion includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



where the value of n is about 1 to about 2 times the value of m and the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight, and the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the copolymer is from about 1:1 to about 1:9.

In some embodiments, the spray dried dispersion includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



where the value of n is 1 to 2 times the value of m and the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of 60:40 by weight, and the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the copolymer is from 1:1 to 1:9.

In some embodiments of the SDDs, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer together form homogeneous particles. In some embodiments, the particles are a substantially homogeneous composition that includes the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer. As used herein, "substantially homogeneous" means that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dispersed as homogeneously as possible throughout the polymer and can be thought of as a solid solution of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, dispersed in the polymer. While the dispersion can have some concentrated domains of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the dispersion itself has a single glass transition temperature (T_g) which demonstrates that the dispersion is substantially homogeneous. This contrasts with a simple physical mixture of pure amorphous particles of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and pure amorphous polymer particles, which generally displays two distinct T_gs, one of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one of the polymer. "T_g," as used herein, is the characteristic temperature where a glassy material, upon gradual heating, undergoes a relatively rapid (e.g., 10 to 100 seconds) physical change from a glass state to a rubber state.

In some embodiments, the particles have a particle size distribution (D-value, D_{50}), of about 5 μm to about 100 μm, such as about 5 μm to about 95 μm, about 5 μm to about 90 μm, about 5 μm to about 85 μm, about 5 μm to about 80 μm, about 5 μm to about 75 μm, about 5 μm to about 70 μm, about 5 μm to about 65 μm, about 5 μm to about 60 μm, about 5 μm to about 55 μm, about 5 μm to about 50 μm, about 5 μm to about 45 μm, about 5 μm to about 40 μm, about 5 μm to about 35 μm, about 5 μm to about 30 μm, about 5 μm to about 25 μm, about 5 μm to about 20 μm, about 5 μm to about 15 μm, about 5 μm to about 10 μm, about 10 μm to about 100 μm, about 10 μm to about 95 μm, about 10 μm to about 90 μm, about 10 μm to

about 85 μm, about 10 μm to about 80 μm, about 10 μm to about 75 μm, about 10 μm to about 70 μm, about 10 μm to about 65 μm, about 10 μm to about 60 μm, about 10 μm to about 55 μm, about 10 μm to about 50 μm, about 10 μm to about 45 μm, about 10 μm to about 40 μm, about 10 μm to about 35 μm, about 10 μm to about 30 μm, about 10 μm to about 25 μm, about 10 μm to about 20 μm, about 10 μm to about 15 μm, about 15 μm to about 100 μm, about 15 μm to about 95 μm, about 15 μm to about 90 μm, about 15 μm to about 85 μm, about 15 μm to about 80 μm, about 15 μm to about 75 μm, about 15 μm to about 70 μm, about 15 μm to about 65 μm, about 15 μm to about 60 μm, about 15 μm to about 55 μm, about 15 μm to about 50 μm, about 15 μm to about 45 μm, about 15 μm to about 40 μm, about 15 μm to about 35 μm, about 15 μm to about 30 μm, about 15 μm to about 25 μm, about 15 μm to about 20 μm, about 20 μm to about 100 μm, about 20 μm to about 95 μm, about 20 μm to about 90 μm, about 20 μm to about 85 μm, about 20 μm to about 80 μm, about 20 μm to about 75 μm, about 20 μm to about 70 μm, about 20 μm to about 65 μm, about 20 μm to about 60 μm, about 20 μm to about 55 μm, about 20 μm to about 50 μm, about 20 μm to about 45 μm, about 20 μm to about 40 μm, about 20 μm to about 35 μm, about 20 μm to about 30 μm, about 20 μm to about 25 μm, about 25 μm to about 100 μm, about 25 μm to about 95 μm, about 25 μm to about 90 μm, about 25 μm to about 85 μm, about 25 μm to about 80 μm, about 25 μm to about 75 μm, about 25 μm to about 70 μm, about 25 μm to about 65 μm, about 25 μm to about 60 μm, about 25 μm to about 55 μm, about 25 μm to about 50 μm, about 25 μm to about 45 μm, about 25 μm to about 40 μm, about 25 μm to about 35 μm, about 25 μm to about 30 μm, about 30 μm to about 100 μm, about 30 μm to about 95 μm, about 30 μm to about 90 μm, about 30 μm to about 85 μm, about 30 μm to about 80 μm, about 30 μm to about 75 μm, about 30 μm to about 70 μm, about 30 μm to about 65 μm, about 30 μm to about 60 μm, about 30 μm to about 55 μm, about 30 μm to about 50 μm, about 30 μm to about 45 μm, about 30 μm to about 40 μm, about 30 μm to about 35 μm, about 35 μm to about 100 μm, about 35 μm to about 95 μm, about 35 μm to about 90 μm, about 35 μm to about 85 μm, about 35 μm to about 80 μm, about 35 μm to about 75 μm, about 35 μm to about 70 μm, about 35 μm to about 65 μm, about 35 μm to about 60 μm, about 35 μm to about 55 μm, about 35 μm to about 50 μm, about 35 μm to about 45 μm, about 35 μm to about 40 μm, about 40 μm to about 100 μm, about 40 μm to about 95 μm, about 40 μm to about 90 μm, about 40 μm to about 85 μm, about 40 μm to about 80 μm, about 40 μm to about 75 μm, about 40 μm to about 70 μm, about 40 μm to about 65 μm, about 40 μm to about 60 μm, about 40 μm to about 55 μm, about 40 μm to about 50 μm, about 40 μm to about 45 μm, about 45 μm to about 100 μm, about 45 μm to about 95 μm,

about 45 μm to about 90 μm, about 45 μm to about 85 μm, about 45 μm to about 80 μm, about 45 μm to about 75 μm, about 45 μm to about 70 μm, about 45 μm to about 65 μm, about 45 μm to about 60 μm, about 45 μm to about 55 μm, about 45 μm to about 50 μm, about 50 μm to about 100 μm, about 50 μm to about 95 μm, about 50 μm to about 90 μm, about 50 μm to about 85 μm, about 50 μm to about 80 μm, about 50 μm to about 75 μm, about 50 μm to about 70 μm, about 50 μm to about 65 μm, about 50 μm to about 60 μm, about 50 μm to about 55 μm, about 55 μm to about 100 μm, about 55 μm to about 95 μm, about 55 μm to about 90 μm, about 55 μm to about 85 μm, about 55 μm to about 80 μm, about 55 μm to about 75 μm, about 55 μm to about 70 μm, about 55 μm to about 65 μm, about 55 μm to about 60 μm, about 60 μm to about 100 μm, about 60 μm to about 95 μm, about 60 μm to about 90 μm, about 60 μm to about 85 μm, about 60 μm to about 80 μm, about 60 μm to about 75 μm, about 60 μm to about 70 μm, about 60 μm to about 65 μm, about 65 μm to about 100 μm, about 65 μm to about 95 μm, about 65 μm to about 90 μm, about 65 μm to about 85 μm, about 65 μm to about 80 μm, about 65 μm to about 75 μm, about 65 μm to about 70 μm, about 70 μm to about 100 μm, about 70 μm to about 95 μm, about 70 μm to about 90 μm, about 70 μm to about 85 μm, about 70 μm to about 80 μm, about 70 μm to about 75 μm, about 75 μm to about 100 μm, about 75 μm to about 95 μm, about 75 μm to about 90 μm, about 75 μm to about 85 μm, about 75 μm to about 80 μm, about 80 μm to about 100 μm, about 80 μm to about 95 μm, about 80 μm to about 90 μm, about 80 μm to about 85 μm, about 85 μm to about 100 μm, about 85 μm to about 95 μm, about 85 μm to about 90 μm, about 90 μm to about 100 μm, about 90 μm to about 95 μm, or about 95 μm to about 100 μm. In some embodiments, the D_{50} is about 5 μm, about 10 μm, about 15 μm, about 16 μm, about 20 μm, about 25 μm, about 30 μm, about 35 μm, about 40 μm, about 45 μm, about 50 μm, about 55 μm, about 60 μm, about 65 μm, about 70 μm, about 75 μm, about 80 μm, about 85 μm, about 90 μm, about 95 μm, or about 100 μm. In some embodiments, the D_{50} is about 10 μm, about 11 μm, about 12 μm, about 13 μm, about 14 μm, about 15 μm, about 16 μm, about 17 μm, about 18 μm, about 19 μm, or about 20 μm, or a value within a range defined by any of the preceding values. In some embodiments, the D_{50} value is about 16 μm. The D_{50} value can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, laser diffraction and disc centrifugation.

In some embodiments, the particles have a particle size distribution (D-value, D_{50}), of 5 μm to 100 μm, such as 5 μm to 95 μm, 5 μm to 90 μm, 5 μm to 85 μm, 5 μm to 80 μm, 5

μm to 75 μm, 5 μm to 70 μm, 5 μm to 65 μm, 5 μm to 60 μm, 5 μm to 55 μm, 5 μm to 50 μm, 5 μm to 45 μm, 5 μm to 40 μm, 5 μm to 35 μm, 5 μm to 30 μm, 5 μm to 25 μm, 5 μm to 20 μm, 5 μm to 15 μm, 5 μm to 10 μm, 10 μm to 100 μm, 10 μm to 95 μm, 10 μm to 90 μm, 10 μm to 85 μm, 10 μm to 80 μm, 10 μm to 75 μm, 10 μm to 70 μm, 10 μm to 65 μm, 10 μm to 60 μm, 10 μm to 55 μm, 10 μm to 50 μm, 10 μm to 45 μm, 10 μm to 40 μm, 10 μm to 35 μm, 10 μm to 30 μm, 10 μm to 25 μm, 10 μm to 20 μm, 10 μm to 15 μm, 15 μm to 100 μm, 15 μm to 95 μm, 15 μm to 90 μm, 15 μm to 85 μm, 15 μm to 80 μm, 15 μm to 75 μm, 15 μm to 70 μm, 15 μm to 65 μm, 15 μm to 60 μm, 15 μm to 55 μm, 15 μm to 50 μm, 15 μm to 45 μm, 15 μm to 40 μm, 15 μm to 35 μm, 15 μm to 30 μm, 15 μm to 25 μm, 15 μm to 20 μm, 20 μm to 100 μm, 20 μm to 95 μm, 20 μm to 90 μm, 20 μm to 85 μm, 20 μm to 80 μm, 20 μm to 75 μm, 20 μm to 70 μm, 20 μm to 65 μm, 20 μm to 60 μm, 20 μm to 55 μm, 20 μm to 50 μm, 20 μm to 45 μm, 20 μm to 40 μm, 20 μm to 35 μm, 20 μm to 30 μm, 20 μm to 25 μm, 25 μm to 100 μm, 25 μm to 95 μm, 25 μm to 90 μm, 25 μm to 85 μm, 25 μm to 80 μm, 25 μm to 75 μm, 25 μm to 70 μm, 25 μm to 65 μm, 25 μm to 60 μm, 25 μm to 55 μm, 25 μm to 50 μm, 25 μm to 45 μm, 25 μm to 40 μm, 25 μm to 35 μm, 25 μm to 30 μm, 30 μm to 100 μm, 30 μm to 95 μm, 30 μm to 90 μm, 30 μm to 85 μm, 30 μm to 80 μm, 30 μm to 75 μm, 30 μm to 70 μm, 30 μm to 65 μm, 30 μm to 60 μm, 30 μm to 55 μm, 30 μm to 50 μm, 30 μm to 45 μm, 30 μm to 40 μm, 30 μm to 35 μm, 35 μm to 100 μm, 35 μm to 95 μm, 35 μm to 90 μm, 35 μm to 85 μm, 35 μm to 80 μm, 35 μm to 75 μm, 35 μm to 70 μm, 35 μm to 65 μm, 35 μm to 60 μm, 35 μm to 55 μm, 35 μm to 50 μm, 35 μm to 45 μm, 35 μm to 40 μm, 40 μm to 100 μm, 40 μm to 95 μm, 40 μm to 90 μm, 40 μm to 85 μm, 40 μm to 80 μm, 40 μm to 75 μm, 40 μm to 70 μm, 40 μm to 65 μm, 40 μm to 60 μm, 40 μm to 55 μm, 40 μm to 50 μm, 40 μm to 45 μm, 45 μm to 100 μm, 45 μm to 95 μm, 45 μm to 90 μm, 45 μm to 85 μm, 45 μm to 80 μm, 45 μm to 75 μm, 45 μm to 70 μm, 45 μm to 65 μm, 45 μm to 60 μm, 45 μm to 55 μm, 45 μm to 50 μm, 50 μm to 100 μm, 50 μm to 95 μm, 50 μm to 90 μm, 50 μm to 85 μm, 50 μm to 80 μm, 50 μm to 75 μm, 50 μm to 70 μm, 50 μm to 65 μm, 50 μm to 60 μm, 50 μm to 55 μm, 55 μm to 100 μm, 55 μm to 95 μm, 55 μm to 90 μm, 55 μm to 85 μm, 55 μm to 80 μm, 55 μm to 75 μm, 55 μm to 70 μm, 55 μm to 65 μm, 55 μm to 60 μm, 60 μm to 100 μm, 60 μm to 95 μm, 60 μm to 90 μm, 60 μm to 85 μm, 60 μm to 80 μm, 60 μm to 75 μm, 60 μm to 70 μm, 60 μm to 65 μm, 65 μm to 100 μm, 65 μm to 95 μm, 65 μm to 90 μm, 65 μm to 85 μm, 65 μm to 80 μm, 65 μm to 75 μm, 65 μm to 70 μm, 70 μm to 100 μm, 70 μm to 95 μm, 70 μm to 90 μm, 70 μm to 85 μm, 70 μm to 80 μm, 70 μm to 75 μm, 75 μm to 100 μm, 75 μm to 95 μm, 75 μm to 90 μm, 75 μm to 85 μm, 75 μm to 80 μm, 80 μm to 100 μm, 80 μm to 95 μm, 80 μm to 90 μm, 80 μm

to 85 μm, 85 μm to 100 μm, 85 μm to 95 μm, 85 μm to 90 μm, 90 μm to 100 μm, 90 μm to 95 μm, or 95 μm to 100 μm. In some embodiments, the D_{50} is 5 μm, 10 μm, 15 μm, 16 μm, 20 μm, 25 μm, 30 μm, 35 μm, 40 μm, 45 μm, 50 μm, 55 μm, 60 μm, 65 μm, 70 μm, 75 μm, 80 μm, 85 μm, 90 μm, 95 μm, or 100 μm. In some embodiments, the D_{50} is 10 μm, 11 μm, 12 μm, 13 μm, 14 μm, 15 μm, 16 μm, 17 μm, 18 μm, 19 μm, or 20 μm, or a value within a range defined by any of the preceding values. In some embodiments, the D_{50} value is 16 μm. The D_{50} value can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, laser diffraction and disc centrifugation.

The SDDs of the present disclosure have a low residual solvent content. "Residual solvent content," as used herein, refers to the amount of solvent present in the SDD following spray drying, immediately upon exit from the spray dryer. The presence of solvent in the SDD lowers the glass transition temperature (T_g) of the dispersion. In some embodiments, mobility of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the SDD and its propensity to phase separate and crystallize decreases as the amount of residual solvent in the SDD decreases. In some embodiments, the SDDs have a residual solvent content of not more than about 10 wt%, such as not more than about 5 wt%, or not more than about 1 wt%. For example, the SDDs have a residual solvent content of about 2 wt%, about 1.9 wt%, about 1.8 wt%, about 1.7 wt%, about 1.6 wt%, about 1.5 wt%, about 1.4 wt%, about 1.3 wt%, about 1.2 wt%, about 1.1 wt%, about 1 wt%, about 0.9 wt%, about 0.8 wt%, about 0.7 wt%, about 0.6 wt%, about 0.5 wt%, or less. In some embodiments, the SDDs have a residual solvent content of less than about 2 wt%. In some embodiments, the SDDs have a residual solvent content of less than about 1 wt%. In some embodiments, the SDDs have a residual solvent content of about 0.5 wt% or less. In some embodiments, the SDDs have a residual solvent content of not more than 10 wt%, such as not more than 5 wt%, or not more than 1 wt%. For example, the SDDs may have a residual solvent content of 2 wt%, 1.9 wt%, 1.8 wt%, 1.7 wt%, 1.6 wt%, 1.5 wt%, 1.4 wt%, 1.3 wt%, 1.2 wt%, 1.1 wt%, 1 wt%, 0.9 wt%, 0.8 wt%, 0.7 wt%, 0.6 wt%, 0.5 wt%, or less. In some embodiments, the SDDs have a residual solvent content of less than 2 wt%. In some embodiments, the SDDs have a residual solvent content of less than 1 wt%. In some embodiments, the SDDs have a residual solvent content of 0.5 wt% or less.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the spray-dried dispersion is substantially amorphous. As used herein,

"substantially amorphous" means that the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in amorphous form is at least 60 wt% and that the amount of crystalline form present does not exceed 20 wt%. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the dispersion is "almost completely amorphous," meaning that at least 90 wt% of the drug is amorphous, or that the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the crystalline form does not exceed 10 wt%. Amounts of crystalline drug can be measured by powder X-ray diffraction (PXRD), scanning electron microscope (SEM) analysis, differential scanning calorimetry (DSC), polarized light microscopy (PLM), or any other standard quantitative or qualitative measurement used to detect crystalline material. Without wishing to be bound by any theory, it is believed that the amorphous, or non-crystalline form, in combination with the polymer, leads to greater ease of dissolution and absorption in the desired location, for example, the intestines, resulting in enhanced bioavailability as compared to a crystalline form of the compound of Formula (I) without polymer.

Process for preparing spray-dried dispersions

Provided in the present disclosure are methods for preparing a spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof, such as the SDDs described herein. In some embodiments, the method includes dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer. In some embodiments, the product obtained by spray-drying is dried to remove the solvent or solvent mixture. In some embodiments, the organic solvent is acetone.

The SDDs disclosed herein can be obtained by spray-drying a mixture comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, one or more polymer(s), and an appropriate solvent or solvent mixture. Spray-drying involves atomization of a liquid mixture containing, for example, a solid and a solvent or solvent mixture, and removal of the solvent or solvent mixture. Atomization can be done, for example, through a two-fluid or pressure or electrosonic nozzle, or on a rotating disk.

Spray-drying converts a liquid feed to a dried particulate form. In some embodiments, spray-drying involves the atomization of a liquid feed solution into a spray of droplets and

contacting the droplets with hot air or gas in a drying chamber. The composition to be spray-dried can be any solution, coarse suspension, slurry, colloidal dispersion, or paste that can be atomized using the selected spray-drying apparatus. In some embodiments, the composition is a solution that is clear and free of undissolved solids. In some embodiments, the sprays are produced by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. Commercially available types of apparatus can be used to conduct the spray-drying. For example, commercial spray dryers are manufactured by Buchi Ltd. and Niro (e.g., the PSD line of spray driers manufactured by Niro). Techniques and methods for spray-drying can also be found in *Perry's Chemical Engineering Handbook*, 6th Ed., R. H. Perry, D. W. Green & J. O. Maloney, eds., McGraw-Hill Book Co. (1984); and Marshall, "Atomization and Spray-Drying" 50, Chem. Eng. Prog. Monogr. Series 2 (1954).

In some embodiments, the spray-drying is conducted with an inlet temperature of from about 40°C to about 100°C, for example, from about 60°C to about 80°C, or from about 70°C to about 75°C. In some embodiments, the spray-drying is conducted with an inlet temperature of about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 70°C, about 72°C, about 75°C, about 80°C, about 85°C, about 90°C, about 95°C, or about 100°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is about 60°C to about 80°C. In some embodiments, the spray-drying is conducted with an inlet temperature of about 61°C, about 63°C, about 65°C, about 67°C, about 69°C, about 71°C, about 73°C, about 75°C, about 77°C, about 79°C, about 81°C, about 83°C, or about 85°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is about 72°C.

In some embodiments, the spray-drying is conducted with an inlet temperature of from 40°C to 100°C, for example, from 60°C to 80°C, or from 70°C to 75°C. In some embodiments, the spray-drying is conducted with an inlet temperature of 40°C, 45°C, 50°C, 55°C, 60°C, 70°C, 72°C, 75°C, 80°C, 85°C, 90°C, 95°C, or 100°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is 60°C to 80°C. In some embodiments, the spray-drying is conducted with an inlet temperature of 61°C, 63°C, 65°C, 67°C, 69°C, 71°C, 73°C, 75°C, 77°C, 79°C, 81°C, 83°C, or 85°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is 72°C.

In some embodiments, the spray-drying is conducted with an outlet temperature of from about 20°C to about 75°C, for example, from about 25°C to about 50°C, or from about 30°C

to about 40°C. In some embodiments, the spray-drying is conducted with an outlet temperature of about 20°C, about 25°C, about 30°C, about 35°C, about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 65°C, about 70°C, or about 75°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is about 25°C to about 45°C. In some embodiments, the spray-drying is conducted with an outlet temperature of about 24°C, about 26°C, about 28°C, about 30°C, about 32°C, about 34°C, about 36°C, about 38°C, about 40°C, about 42°C, about 44°C, or about 46°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is about 35°C.

In some embodiments, the spray-drying is conducted with an outlet temperature of from 20°C to 75°C, for example, from 25°C to 50°C, or from 30°C to 40°C. In some embodiments, the spray-drying is conducted with an outlet temperature of 20°C, 25°C, 30°C, 35°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, or 75°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is 25°C to 45°C. In some embodiments, the spray-drying is conducted with an outlet temperature of 24°C, 26°C, 28°C, 30°C, 32°C, 34°C, 36°C, 38°C, 40°C, 42°C, 44°C, or 46°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is 35°C.

In some embodiments, the method involves removing the organic solvent after formation of the spray-dried dispersion. In some embodiments, the organic solvent is removed by drying the SDD. In some embodiments, a secondary drying process, such as fluidized bed drying, vacuum drying, tray drying, microwave drying, rotary drum drying or biconical vacuum drying is used to remove or reduce residual solvents, such as the organic solvent, to pharmaceutically acceptable levels. In some embodiments, the SDD is dried with a convection tray dryer.

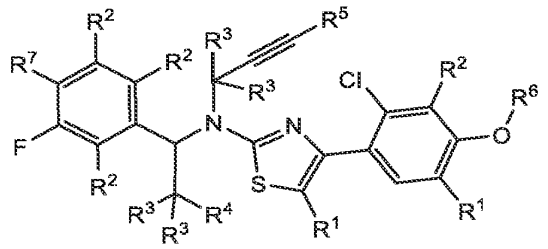
In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of less than about 0.2 g/mL, or less than about 0.15 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of about 0.19 g/mL, about 0.18 g/mL, about 0.17 g/mL, about 0.16 g/mL, about 0.15 g/mL, about 0.14 g/mL, about 0.13 g/mL, about 0.12 g/mL, about 0.11 g/mL, about 0.1 g/mL, about 0.09 g/mL, about 0.08 g/mL, about 0.07 g/mL, about 0.06 g/mL or about 0.05 g/mL, or within a range defined by any of the preceding values. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of less than 0.2 g/mL, or less than 0.15 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density

of 0.19 g/mL, 0.18 g/mL, 0.17 g/mL, 0.16 g/mL, 0.15 g/mL, 0.14 g/mL, 0.13 g/mL, 0.12 g/mL, 0.11 g/mL, 0.1 g/mL, 0.09 g/mL, 0.08 g/mL, 0.07 g/mL, 0.06 g/mL or 0.05 g/mL, or within a range defined by any of the preceding values. The term "bulk density," as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume.

In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of less than about 0.3 g/mL, or less than about 0.25 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of about 0.29 g/mL, about 0.28 g/mL, about 0.27 g/mL, about 0.26 g/mL, about 0.25 g/mL, about 0.24 g/mL, about 0.23 g/mL, about 0.22 g/mL, about 0.21 g/mL, about 0.2 g/mL, or about 0.19 g/mL, or within a range defined by any of the preceding values. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of less than 0.3 g/mL, or less than 0.25 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of 0.29 g/mL, 0.28 g/mL, 0.27 g/mL, 0.26 g/mL, 0.25 g/mL, 0.24 g/mL, 0.23 g/mL, 0.22 g/mL, 0.21 g/mL, 0.2 g/mL, or 0.19 g/mL, or within a range defined by any of the preceding values. The term "tap density" or "tapped density," as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

Deuterated Compounds

Also disclosed herein are compounds having the structure of the following formula (II):



(II)

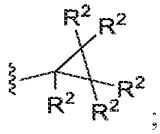
or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently $C(R^A)_3$;

each R^A is independently hydrogen or deuterium;

each R^2 is independently hydrogen or deuterium;

each R^3 is independently hydrogen or deuterium;

R^4 is  ;

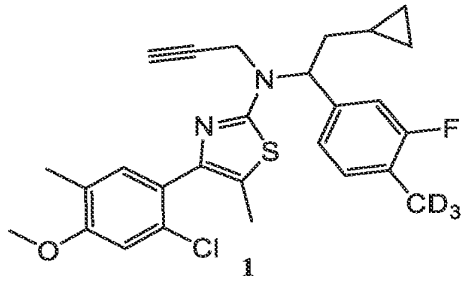
R^5 is hydrogen or deuterium;

R^6 is $C(R^A)_3$; and

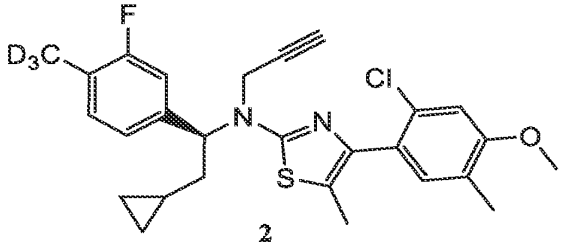
R^7 is $C(R^B)_3$, wherein at least one of R^A, R^B, R^2, R^3 and R^5 is deuterium.

With regard to the compounds provided herein, when a particular atomic position is designated as having deuterium or "D" or "d", it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of, in certain embodiments, at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation) at each designated deuterium position.

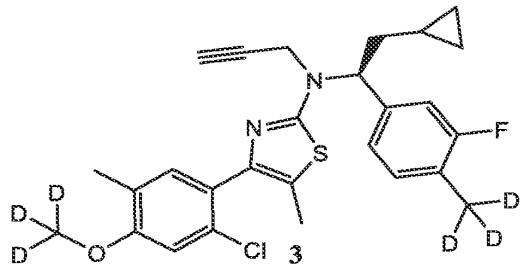
In some embodiments, the compound of Formula (II) may be one of the following, or a pharmaceutically acceptable salt thereof:



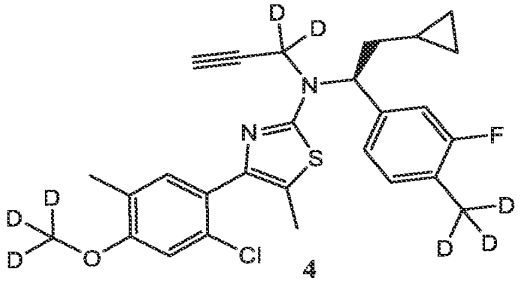
1



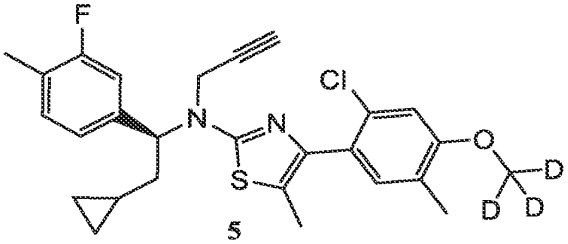
2



3



4



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Pharmaceutical compositions

The methods and uses disclosed herein can comprise administering the compound of Formula (I) as a pharmaceutical composition.

In some embodiments of the methods described herein, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition further comprising one or more pharmaceutically acceptable excipients.

Also provided herein is a pharmaceutical composition comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in any of the methods described herein.

In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that does not comprise a spray-dried dispersion of the compound

of Formula (I), as specified, e.g., in Example 1. Accordingly, in some embodiments, the pharmaceutical composition does not comprise any of the following polymers: hydroxypropylmethylcellulose acetate succinate-L (HPMCAS-L); polyvinyl pyrrolidone vinyl acetate 64 (PVP/VA 64); HPMCAS-M; and methyl methacrylate copolymer (1:1) (Eudragit® L100).

In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is not the reference formulation described in Example 9. Accordingly, in some embodiments, the pharmaceutical composition does not comprise at least three of the excipients selected from caprylic/capric triglyceride (Labrafac® Lipophile, Gattefossé, France); propylene glycol dicrapolate/dicaprate (Labrafac® PG, Gattefossé, France); oleoyl polyoxyl-6 glycerides (Labrafil® M 1944 CS, Gattefossé, France); polysorbate 20; polyoxyl castor oil (Kolliphor® RH 40, BASF, Germany); polyoxyl 15 hydroxystearate (Kolliphor® HS 15, BASF, Germany); lauroyl polyoxyl-32 glycerides (Gelucire® 44/14, Gattefossé, France); d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS); and diethylene glycol monoethyl ether (Transcutol®, Gattefossé, France).

In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 9. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 11. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 12. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 13.

In some embodiments, the pharmaceutical compositions include a spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition includes the SDD comprising a compound of Formula (I) and one or more pharmaceutically acceptable excipients. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 20% to about 90% w/w of the composition, such as about 20% to about 85%, about 20% to about 80%, about 20% to about 75%, about 20% to about 70%, about 20% to about 65%, about 20% to about 60%, about 20% to about 55%, about 20% to about 50%, about 20% to about 45%, about 20% to about 40%, about 20% to about 35%, about 20% to about 30%, about 20%

to about 25%, about 25% to about 90%, about 25% to about 85%, about 25% to about 80%, about 25% to about 75%, about 25% to about 70%, about 25% to about 65%, about 25% to about 60%, about 25% to about 55%, about 25% to about 50%, about 25% to about 45%, about 25% to about 40%, about 25% to about 35%, about 25% to about 30%, about 30% to about 90%, about 30% to about 85%, about 30% to about 80%, about 30% to about 75%, about 30% to about 70%, about 30% to about 65%, about 30% to about 60%, about 30% to about 55%, about 30% to about 50%, about 30% to about 45%, about 30% to about 40%, about 30% to about 35%, about 35% to about 90%, about 35% to about 85%, about 35% to about 80%, about 35% to about 75%, about 35% to about 70%, about 35% to about 65%, about 35% to about 60%, about 35% to about 55%, about 35% to about 50%, about 35% to about 45%, about 35% to about 40%, about 40% to about 90%, about 40% to about 85%, about 40% to about 80%, about 40% to about 75%, about 40% to about 70%, about 40% to about 65%, about 40% to about 60%, about 40% to about 55%, about 40% to about 50%, about 40% to about 45%, about 45% to about 90%, about 45% to about 85%, about 45% to about 80%, about 45% to about 75%, about 45% to about 70%, about 45% to about 65%, about 45% to about 60%, about 45% to about 55%, about 45% to about 50%, about 50% to about 90%, about 50% to about 85%, about 50% to about 80%, about 50% to about 75%, about 50% to about 70%, about 50% to about 65%, about 50% to about 60%, about 50% to about 55%, about 55% to about 90%, about 55% to about 85%, about 55% to about 80%, about 55% to about 75%, about 55% to about 70%, about 55% to about 65%, about 55% to about 60%, about 60% to about 90%, about 60% to about 85%, about 60% to about 80%, about 60% to about 75%, about 60% to about 70%, about 60% to about 65%, about 65% to about 90%, about 65% to about 85%, about 65% to about 80%, about 65% to about 75%, about 65% to about 70%, about 70% to about 90%, about 70% to about 85%, about 70% to about 80%, about 70% to about 75%, about 75% to about 90%, about 75% to about 85%, about 75% to about 80%, about 80% to about 90%, about 80% to about 85%, or about 85% to about 90% w/w of the composition. In some embodiments, the SDD is present in an amount of about 40% to about 90% w/w of the composition. In some embodiments, the SDD is present in an amount of about 40% to about 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 60% to about 80% w/w of the composition. In some embodiments, the SDD is present in an amount of about 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 1% to about 20% w/w of the composition, such as about 13% w/w of the composition.

In some embodiments, the pharmaceutical composition includes the SDD comprising a compound of Formula (I) and one or more pharmaceutically acceptable excipients. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of 20% to 90% w/w of the composition, such as 20% to 85%, 20% to 80%, 20% to 75%, 20% to 70%, 20% to 65%, 20% to 60%, 20% to 55%, 20% to 50%, 20% to 45%, 20% to 40%, 20% to 35%, 20% to 30%, 20% to 25%, 25% to 90%, 25% to 85%, 25% to 80%, 25% to 75%, 25% to 70%, 25% to 65%, 25% to 60%, 25% to 55%, 25% to 50%, 25% to 45%, 25% to 40%, 25% to 35%, 25% to 30%, 30% to 90%, 30% to 85%, 30% to 80%, 30% to 75%, 30% to 70%, 30% to 65%, 30% to 60%, 30% to 55%, 30% to 50%, 30% to 45%, 30% to 40%, 30% to 35%, 35% to 90%, 35% to 85%, 35% to 80%, 35% to 75%, 35% to 70%, 35% to 65%, 35% to about 60%, 35% to 55%, 35% to 50%, 35% to 45%, 35% to 40%, 40% to 90%, 40% to 85%, 40% to 80%, 40% to 75%, 40% to 70%, 40% to 65%, 40% to 60%, 40% to 55%, 40% to 50%, 40% to 45%, 45% to 90%, 45% to 85%, 45% to 80%, 45% to 75%, 45% to 70%, 45% to 65%, 45% to 60%, 45% to 55%, 45% to 50%, 50% to 90%, 50% to 85%, 50% to 80%, 50% to 75%, 50% to 70%, 50% to 65%, 50% to 60%, 50% to 55%, 55% to 90%, 55% to 85%, 55% to 80%, 55% to 75%, 55% to 70%, 55% to 65%, 55% to 60%, 60% to 90%, 60% to 85%, 60% to 80%, 60% to 75%, 60% to 70%, 60% to 65%, 65% to 90%, 65% to 85%, 65% to 80%, 65% to 75%, 65% to 70%, 70% to 90%, 70% to 85%, 70% to 80%, 70% to 75%, 75% to 90%, 75% to 85%, 75% to 80%, 80% to 90%, 80% to 85%, or about 85% to 90% w/w of the composition. In some embodiments, the SDD is present in an amount of 40% to 90% w/w of the composition. In some embodiments, the SDD is present in an amount of 40% to 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of 60% to 80% w/w of the composition. In some embodiments, the SDD is present in an amount of 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 1% to about 20% w/w of the composition, such as about 13% w/w of the composition.

In some embodiments of the pharmaceutical compositions disclosed herein (e.g., a composition including an SDD), the pharmaceutically acceptable excipient is selected from the group consisting of a filler, a lubricant, and combinations thereof. In some embodiments, the pharmaceutical excipients are selected from the group consisting of a glidant, a filler, a disintegrant, a lubricant, and a combination thereof.

In some embodiments, the pharmaceutical composition includes a filler. In some embodiments, the filler is selected from among binders, diluents, disintegrants, glidants, surfactants, and combinations thereof.

In some embodiments, the filler include saccharides (e.g., sugars, starch, and cellulose), gelatin, calcium carbonate, and synthetic polymers (e.g., polyvinylpyrrolidone, polyethylene glycol, and poloxamers (e.g., Poloxamer 188, a copolymer of polyoxyethylene and polyoxypropylene)). Exemplary fillers include, but are not limited to, glucose, sucrose, lactose, a starch, including modified starches such as sodium starch glycolate (e.g., Explotab®), xylitol, dextrin, saccharose, sorbitol, mannitol (e.g., Parteck® M 200 (mannitol with an average particle size of about 50 μm to about 500 μm) or Parteck® M 100 (mannitol with an average particle size of less than 212 μm)), a cellulose, a polyvinylpyrrolidone, a polyethylene glycol, a polyvinyl alcohol, a polymethacrylate, dibasic calcium phosphate, magnesium stearate, calcium stearate, sodium stearate, stearic acid, hydrogenated vegetable oils, a mineral oil, sodium lauryl sulfate, magnesium lauryl sulfate, glyceryl palmitostearate, sodium benzoate, sodium stearyl fumarate, colloidal silicon dioxide, sodium benzoate, sodium oleate, sodium acetate, aliginic acid, alginates (e.g., sodium alginate), calcium silicate, and ion exchange resins. Exemplary cellulose fillers include microcrystalline cellulose (e.g., Avicel® PH-101 (microcrystalline cellulose with an average particle size of approximately 50 μm) or Avicel® PH 200 (microcrystalline cellulose with an average particle size of approximately 180 μm)), methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethylcellulose. Exemplary fillers include cross-linked polyvinylpyrrolidone such as with an average particle size of 90 μm to 130 μm) or with an average particle size of 10 μm to 30 μm). Other fillers known to those of skill in the art are also contemplated as being useful when formulated in the pharmaceutical compositions described herein.

In some embodiments, the filler is a binder. Binders include agents that hold the active pharmaceutical ingredient (e.g., spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof) and inactive ingredients together in a cohesive mix. Exemplary binders include, but are not limited to, glucose, sucrose, lactose, a starch, including modified starches such as sodium starch glycolate (Explotab®), xylitol, dextrin, saccharose, sorbitol, mannitol (e.g., Parteck® M 200 (mannitol with an average particle size of about 50 μm to about 500 μm), Parteck® M 100 (mannitol with an average particle size of less than 212 μm)), gelatin, gum tragacanth, acacia mucilage, a cellulose, a polyvinylpyrrolidone, a polyethylene glycol, a polyvinyl alcohol, a

polymethacrylate, and sodium starch glycolate. Exemplary cellulose fillers include microcrystalline cellulose (e.g., Avicel® PH-101 (microcrystalline cellulose with an average particle size of approximately 50 μm) or Avicel® PH 200 (microcrystalline cellulose with an average particle size of approximately 180 μm)), cellulose ethers, methyl cellulose, ethyl cellulose, croscarmellose sodium, sodium carboxy methyl cellulose starches, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose. Exemplary polyvinylpyrrolidone fillers include cross-linked polyvinylpyrrolidone such as Kollidon® CL (crospovidone with an average particle size of 90 μm to 130 μm) or Kollidon® CL-SF (crospovidone with an average particle size of 10 μm to 30 μm). Other binders known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

In some embodiments, the filler is a diluent. Suitable diluents include, but are not limited to, lactose, mannitol, isomalt, sucrose, dextrose, and sorbitol.

In some embodiments, the filler is a disintegrant. Disintegrants include any agent that promotes breakup of the formulation in an aqueous environment, for example, to promote more rapid release of the active pharmaceutical ingredient (e.g., the compound of Formula (I), or a pharmaceutically acceptable salt thereof). Exemplary disintegrants include, but are not limited to, starch and modified starches, such as corn starch, potato starch, sodium starch glycolate or croscarmellose sodium, alginic acid, alginates, such as sodium alginate, polyvinylpyrrolidone, bentonite, methylcellulose, agar, carboxymethylcellulose, crospovidone, acid-carbonate effervescent systems, such as citric acid with bicarbonate salts, and ion exchange resins. Other disintegrants known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

In some embodiments, the pharmaceutical composition comprises a disintegrant. In some embodiments, the pharmaceutical composition comprises about 1 w/w% to about 30 w/w% of the disintegrant. In some embodiments, the pharmaceutical composition comprises about 5 w/w% to about 15 w/w% of the disintegrant. In some embodiments, the pharmaceutical composition comprises about 10 w/w% of the disintegrant. In some embodiments, the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, and sodium bicarbonate. In some embodiments, the disintegrant is croscarmellose sodium.

In some embodiments, the filler is a glidant. Glidants can be used to improve the flowability of a powder or granules or both. Glidants include, but are not limited to, silicone dioxide, such as colloidal silicon dioxide or hydrated silicon dioxide, magnesium silicate,

magnesium aluminometasilicate, talc, starch, calcium silicate, light anhydrous silicic acid, and silicon dioxide aerogels.

In some embodiments, the pharmaceutical composition comprises a glidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 5 w/w% of the glidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 1 w/w% of the glidant. In some embodiments, the pharmaceutical composition comprises about 0.67 w/w% of the glidant. In some embodiments, the glidant is selected from calcium silicate, silicon dioxide, and talc. In some embodiments, the glidant is calcium silicate.

In some embodiments, the filler is a surfactant, wetting agent, solubilizer, or combination thereof. Examples include, but are not limited to, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., Tween®), polyoxyethylene stearates, sodium dodecylsulfate, tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton). Other examples include, but are not limited to, poloxamers such as Pluronic® F68, F127, and F108, which are block copolymers of ethylene oxide and propylene oxide, and polyxamines such as Tetronic® 908 (also known as Poloxamine® 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (available from BASF), dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol® OT, which is a dioctyl ester of sodium sulfosuccinic acid (available from American Cyanimid), Duponol® P, which is a sodium lauryl sulfate (available from DuPont), Triton® X-200, which is an alkyl aryl polyether sulfonate (available from Rohm and Haas), Tween® 20 and Tween® 80, which are polyoxyethylene sorbitan fatty acid esters (available from ICI Specialty Chemicals), Carbowax™ 3550 and 934, which are polyethylene glycols (available from Union Carbide), Crodesta™ F-110, which is a mixture of sucrose stearate and sucrose distearate, and Crodesta™ SL-40 (both available from Croda Inc.), and SA90HCO, which has the chemical formula $C_{18}H_{37}—CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$.

In some embodiments, the pharmaceutical composition comprises a filler. In some embodiments, the pharmaceutical composition comprises about 30 w/w% to about 99 w/w% of the filler. In some embodiments, the pharmaceutical composition comprises about 50 w/w% to about 90 w/w% of the filler. In some embodiments, the pharmaceutical composition comprises about 75.5 w/w% of the filler. In some embodiments, the filler is selected from

mannitol, microcrystalline cellulose, lactose, starch, isomalt, silicified microcrystalline cellulose, Dicalcium Phosphate, maltodextrin, and a combination thereof. In some embodiments, the filler is a combination of mannitol and microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 30 w/w% to about 80 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 50 w/w% to about 60 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 56 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 1 w/w% to about 50 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 10 w/w% to about 30 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 20 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose.

In some embodiments, the pharmaceutical composition includes a lubricant. Lubricants are agents added to pharmaceutical formulations to reduce friction during processing and prevent ingredients from clumping together. Exemplary lubricants include, but are not limited to, talc, starch, magnesium stearate, calcium stearate, sodium stearate, zinc stearate, stearic acid, vegetable stearin, adipic acid, waxy fatty acids, such as glyceryl behenate, a hydrogenated vegetable oil, a mineral oil, a polyethylene glycol, lycopodium, sodium lauryl sulfate, magnesium lauryl sulfate, glyceryl palmitostearate, sodium benzoate, sodium chloride, sterotex, glycerol monostearate, sodium stearyl fumarate, colloidal silicon dioxide, sodium benzoate, sodium oleate, and sodium acetate. Other lubricants known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

In some embodiments, the pharmaceutical composition comprises a lubricant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 10 w/w% of the lubricant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 1 w/w% of the lubricant. In some embodiments, the pharmaceutical composition comprises about 0.5 w/w% of the lubricant. In some embodiments, the pharmaceutical lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid sodium lauryl sulfate, sodium oleate, glyceryl behenate, and talc. In some embodiments, the lubricant is sodium stearyl fumarate.

In some embodiments, the pharmaceutical composition comprises:

(a) the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;

(b) a glidant;

(c) a filler; and

(d) a disintegrant.

In some embodiments, the pharmaceutical composition comprises:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;

(b) about 0.1 w/w% to about 1 w/w% of a glidant;

(c) about 50 w/w% to about 90 w/w% of a filler; and

(d) about 5 w/w% to about 0.2 w/w% of a disintegrant.

In some embodiments, the pharmaceutical composition comprises:

(a) about 13 w/w% of the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;

(b) about 0.67 w/w% of a glidant;

(c) about 75.5 w/w% of a filler; and

(d) about 10 w/w% of a disintegrant.

In some embodiments, the pharmaceutical composition comprises:

(a) the spray-dried dispersion of Example 3;

(b) calcium silicate;

(c) a combination of mannitol and microcrystalline cellulose; and

(d) croscarmellose sodium.

In some embodiments, the pharmaceutical composition comprises:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of Example 3;

(b) about 0.1 w/w% to about 1 w/w% of calcium silicate;

(c) about 50 w/w% to about 60 w/w% of mannitol and about 10 w/w% to about 30 w/w% of microcrystalline cellulose; and

(d) about 5 w/w% to about 0.2 w/w% of croscarmellose sodium.

In some embodiments, the pharmaceutical composition comprises:

(a) about 13 w/w% of the spray-dried dispersion of Example 3;

(b) about 0.67 w/w% of calcium silicate;

(c) about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose; and

(d) about 10 w/w% of croscarmellose sodium.

Additional excipients can be included in the pharmaceutical formulations of the present disclosure. Further examples of excipients include, but are not limited to, pigments, colorants, flavoring agents, preservatives, and sweeteners. Flavors and colors can be added to improve the taste or appearance of a formulation. Examples of preservatives used in pharmaceutical compositions are aromatic alcohols, such as benzyl or phenol alcohol, antioxidants such as vitamin A, vitamin E, vitamin C, and selenium, amino acids such as cysteine and methionine, citric acid and sodium citrate, or synthetic preservatives such as methyl paraben and propyl paraben. Sweeteners can be added to make the ingredients more palatable, especially in chewable tablets or liquids like syrups.

Also provided are methods for preparing a pharmaceutical composition, such as a pharmaceutical composition of the present disclosure. In some embodiments, the method includes combining the spray-dried dispersion described herein with one or more pharmaceutically acceptable excipients, e.g., a pharmaceutically acceptable excipient described herein.

In some embodiments, the method for preparing the pharmaceutical composition comprises:

(a) blending the spray-dried dispersion described herein, with a glidant;

(b) further blending the blend of step (a) with a filler and a disintegrant;

(c) screening the blend of step (b) to break up aggregates and assist with blend uniformity;

(d) further blending the intragranular blend of step (c);

(e) compaction of the intragranular blend of step (d) via roller compaction to form granules; and

(f) milling of ribbon from roller compaction into granules of step (e).

In some embodiments, the spray-dried dispersion is the spray-dried dispersion described in Example 3.

The pharmaceutical compositions of the present disclosure are formulated for oral administration. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media can be employed. For solid oral preparations such as, for example, powders, capsules, caplets, gelcaps, and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Oral pharmaceutical dosage forms can be solid, gel, or liquid. In some embodiments, the dosage form is a solid dosage form. In some embodiments, the solid dosage form is a pill, tablet, capsule, caplet, gelcaps, granules, powder, sachet, melting strip, or melting film. In some embodiments, the solid dosage form is coated. In some embodiments, the coating is an enteric coating, a sugar coating, or a film coating. In some embodiments, the solid dosage form is a coated particle, coated tablet, enterocoated tablet, or enterocoated capsule. In some embodiments, the solid dosage form is a pill or tablet. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric coated, sugar coated or film coated. In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a powder, solution, or suspension (e.g., in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides), or is encapsulated in a capsule (gelatin or cellulose base capsule). Capsules can be hard or soft gelatin capsules, while granules and powders can be provided in non-effervescent or effervescent form with a combination of other ingredients known to those skilled in the art.

The pharmaceutical compositions of the present disclosure can contain, per dosage unit, e.g., tablet, capsule, powder, and the like, an amount of the active ingredient necessary to deliver an effective dose as described above.

In some embodiments, the pharmaceutical compositions of the present disclosure are formulated in unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg in the unit dosage form. For example, about 5 mg to about 175 mg, about 5 mg to about 150 mg, about 5 mg to about 125 mg, about 5 mg to about 100 mg, about 5 mg to about 75 mg,

about 5 mg to about 50 mg, about 5 mg to about 25 mg, about 25 mg to about 200 mg, about 25 mg to about 175 mg, about 25 mg to about 150 mg, about 25 mg to about 125 mg, about 25 mg to about 100 mg, about 25 mg to about 75 mg, about 25 mg to about 50 mg, about 50 mg to about 200 mg, about 50 mg to about 175 mg, about 50 mg to about 150 mg, about 50 mg to about 125 mg, about 50 mg to about 100 mg, about 50 mg to about 75 mg, about 75 mg to about 200 mg, about 75 mg to about 175 mg, about 75 mg to about 150 mg, about 75 mg to about 125 mg, about 75 mg to about 100 mg, about 100 mg to about 200 mg, about 100 mg to about 175 mg, about 100 mg to about 150 mg, about 100 mg to about 125 mg, about 125 mg to about 200 mg, about 125 mg to about 175 mg, about 125 mg to about 150 mg, about 150 mg to about 200 mg, about 150 mg to about 175 mg, or about 175 mg to about 200 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg to about 125 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg, about 10 mg, about 25 mg, about 35 mg, about 50 mg, about 65 mg, about 75 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, or about 200 mg in the unit dosage form, or within a range defined by any of the preceding values. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg in the unit dosage form. . In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 5 mg to 250 mg in the unit dosage form. For example, 5 mg to 175 mg, 5 mg to 150 mg, 5 mg to 125 mg, 5 mg to 100 mg, 5 mg to 75 mg, 5 mg to 50 mg, 5 mg to 25 mg, 25 mg to 200 mg, 25 mg to 175 mg, 25 mg to 150 mg, 25 mg to 125 mg, 25 mg to 100 mg, 25 mg to 75 mg, 25 mg to 50 mg, 50 mg to 200 mg, 50 mg to 175 mg, 50 mg to 150 mg, 50 mg to 125 mg, 50 mg to 100 mg, 50 mg to 75 mg, 75 mg to 200 mg, 75 mg to 175 mg, 75 mg to 150 mg, 75 mg to 125 mg, 75 mg to 100 mg, 100 mg to 200 mg, 100 mg to 175 mg, 100 mg to 150 mg, 100 mg to 125 mg, 125 mg to 200 mg, 125 mg to 175 mg, 125 mg to 150 mg, 150 mg to 200 mg, 150 mg to 175 mg, or 175 mg to 200 mg in the unit dosage form. In some embodiments, the

compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 25 mg to 125 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 75 mg to 150 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 5 mg, 10 mg, 25 mg, 35 mg, 50 mg, 65 mg, 75 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg in the unit dosage form, or within a range defined by any of the preceding values. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 50 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 100 mg in the unit dosage form. In some embodiments, the pharmaceutical compositions of the present disclosure are formulated as a tablet. In some embodiments, the tablet is coated. In some embodiments, the pharmaceutical compositions of the present disclosure are formulated as capsules. In some embodiments, the pharmaceutical compositions are in sachet form. In some embodiments, the pharmaceutical compositions are in granule form.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 25 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 75 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 100 mg, based on the weight of the free base.

In some embodiments, the pharmaceutical composition is administered in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

In some embodiments, the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

The daily dosage of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition as described in the present disclosure can be varied over a wide range from about 1.0 mg to about 10,000 mg per adult human per day, or higher, or any range therein. For oral administration, the compositions can be provided in the form of tablets containing, for example, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2.5 mg, about 5.0 mg, about 10.0 mg, about 15.0 mg, about 25.0 mg, about 50.0 mg, about 75.0 mg, about 100 mg, about 150 mg, about 200 mg, about 250 or about 500 milligrams of the compound of Formula (I), or pharmaceutically acceptable salt thereof, for the symptomatic adjustment of the dosage to the subject to be treated. In some embodiments, an effective amount of the compound of Formula (I), or pharmaceutically acceptable salt thereof, can be supplied at a dosage level of from about 0.1 mg/kg to about 1000 mg/kg of body weight per day, or any range therein, for example, the range can be from about 0.5 mg/kg to about 500 mg/kg, about 1.0 mg/kg to about 250 mg/kg, about 0.1 mg/kg to about 100 mg/kg, about 0.1 mg/kg to about 50.0 mg/kg of body weight per day, about 0.1 mg/kg to about 15.0 mg/kg of body weight per day, about 0.5 mg/kg to about 7.5 mg/kg of body weight per day, or any amount to range therein. In some embodiments, an effective amount of the compound of Formula (I), or pharmaceutically acceptable salt thereof, can be supplied at a dosage level of from 0.1 mg/kg to 1000 mg/kg of body weight per day, or any range therein, for example, the range can be from 0.5 mg/kg to 500 mg/kg, 1.0 mg/kg to 250 mg/kg, 0.1 mg/kg to 100 mg/kg, 0.1 mg/kg to 50.0 mg/kg of body weight per day, 0.1 mg/kg to 15.0 mg/kg of body weight per day, 0.5 mg/kg to 7.5 mg/kg of body weight per day, or any amount to range therein. A pharmaceutical composition as provided herein can be administered on a regimen of 1 to 4 times per day or in a single daily dose.

In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 25 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 50 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 75 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 100 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 150 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 200 mg, based on the weight of the free base.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 25 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 75 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 100 mg, based on the weight of the free base.

In some embodiments, the daily dose of the pharmaceutical composition is about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the

pharmaceutical composition is about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some

embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof, twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

Factors associated with the particular subject being treated, including subject age, weight, diet, and time of administration, can result in the need to adjust dosages. In some embodiments, the subject is a human adult. In some embodiments, the subject is a pediatric subject.

One skilled in the art will recognize that both *in vivo* and *in vitro* trials using suitable, known, and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder. One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy subjects and/or those suffering from a given disorder, can be completed according to methods well known in the clinical and medical arts. For example, determining proper dosages for pediatric subjects can be determined using known methods, including weight, age, and models such as Simcyp® Pediatric Simulation modeling (CERTARA, Princeton, N.J.) which can be used to establish a pharmacokinetic approach for dosing that takes into account subject age, ontogeny of the clearance pathways that a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and body surface area (BSA).

In some embodiments, the pharmaceutical compositions of the present disclosure are stable for at least 3 months. In some embodiments, the pharmaceutical compositions are stable for at least 6 months. In some embodiments, the pharmaceutical compositions are stable for at least 9 months. In some embodiments, the pharmaceutical compositions are stable for at least 12 months. For example, the compositions do not exhibit a change (e.g., greater than 5%) in appearance, pH, percent impurities, activity (as measured by in vitro assays), or osmolarity over time, e.g., at least 3 months, 6 months, 9 months, or at least 12 months as compared to the original composition after manufacturing. In some embodiments, the pharmaceutical compositions do not exhibit a significant change, as defined by the International Conference

on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in one or more of appearance, pH, percent impurities, activity (as measured by *in vitro* assays), or osmolarity over time, e.g., at least 12 months as compared to the original pharmaceutical composition after manufacturing.

Kits

Also provided are kits. Typically, a kit includes one or more pharmaceutical compositions as described herein, e.g., a pharmaceutical composition containing, e.g., a spray-dried dispersion as described in Examples 1-4, or the formulation described in Example 9. In certain embodiments, a kit can include one or more delivery systems, e.g., for delivering or administering the pharmaceutical composition as provided herein, and directions for use of the kit (e.g., instructions for treating a subject). In some embodiments, the kit can include a pharmaceutical composition as described herein and a label that indicates that the contents are to be administered to a subject with congenital adrenal hyperplasia. The actual dose of the compound of Formula (I), or pharmaceutically acceptable salt thereof, provided herein depends on the specific formulation, the weight of the patient, and on the condition to be treated.

EXAMPLES

Example 1: Spray-dried dispersion formulations containing the compound of Formula (I) and various polymers

Spray-dried dispersion formulations

A series of spray-dried dispersion (SDD) formulations containing the compound of Formula (I) and a polymer were prepared. The SDD formulations included: (1) 10% compound of Formula (I)/90% hydroxypropylmethylcellulose acetate succinate-L (HPMCAS-L); (2) 25% compound of Formula (I)/75% HPMCAS-L; (3) 40% compound of Formula (I)/60% HPMCAS-L; (4) 25% compound of Formula (I)/75% polyvinyl pyrrolidone vinyl acetate 64 (PVP/VA 64); (5) 25% compound of Formula (I)/60% Cabosil (fumed silica)/15% HPMCAS-L; (6) 25% compound of Formula (I)/75% HPMCAS-M; and (7) 25% compound of Formula (I)/75% methyl methacrylate copolymer (1:1) (Eudragit® L100).

The PVP/VA polymer was a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate with a ratio of 60:40 by weight 1-vinyl-2-pyrrolidone:vinyl acetate with an average molecular weight of 45,000-70,000 (copovidone, sold as Kollidon® VA 64, BASF, Florham Park, NJ). The HPMCAS was a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose that was either grade L (HPMCAS-L), with an acetyl content of 5-9%, a succinoyl content of 14-18%, a methoxyl content of 20-24%, and a hydroxypropoxy content of 5-9% (sold by Shin-Etsu, Japan); or grade M (HPMCAS-M), with an acetyl content of 7-11%, a succinoyl content of 10-14%, a methoxyl content of 21-25%, and a hydroxypropoxy content of 5-9% (sold by Shin-Etsu, Japan).

Dissolution performance

Dissolution performance of several of the SDD formulations described above was tested (see FIG. 1). 1000 µgA/mL of each SDD was tested in 0.5 wt% simulated intestinal fluid (SIF) in PBS, pH 6.5. Samples were tested at 5, 10, 20, 45, 90, and 1200 minutes. A lipid formulation containing 10% of the compound of Formula (I) was used as a control. The results are shown in Table 4, below.

Table 4. Dissolution data of various SDDs

Sample	C_{max90} (µg/mL)	AUC_{90} (min*µg/mL)	C_{max90} (µg/mL)	$Ultra_{90}$ (µg/mL)	C_{1200} (µg/mL)	$Ultra_{1200}$ (µg/mL)
2	762	66,080	743	210	671	166
4	322	27,330	306	109*	268	199
6	718	62,240	708	202	632	217
7	742	60,600	742	113*	674	194
Control	802	69,580	800	253	799	270

*Large variability between replicates, high value discarded

Non-sink dissolution

A membrane flux assay was performed (see, e.g., Stewart et al., Mol. Pharm. (2017) 14:2032-2046) and non-sink dissolution data was collected for several of the SDD formulations described above and compared to the compound of Formula (I) and several reference formulations, including a semi-solid lipidic formulation (Reference Formulation 1) and two self-emulsifying drug delivery system (SEDDS) formulations (Reference Formulations 2 and 3). The components of the Reference Formulations are shown in Table 5, below, and include, in addition to the compound of Formula (I), caprylic/capric triglyceride (Labrafac® Lipophile, Gattefossé, France); propylene glycol dicrapolate/dicaprate (Labrafac® PG, Gattefossé, France); oleoyl polyoxyl-6 glycerides (Labrafil® M 1944 CS, Gattefossé, France); polysorbate 20; polyoxyl castor oil (Kolliphor® RH 40, BASF, Germany); polyoxyl 15 hydroxystearate (Kolliphor® HS 15, BASF, Germany); lauroyl polyoxyl-32 glycerides (Gelucire® 44/14, Gattefossé, France); d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS); and diethylene glycol monoethyl ether (Transcutol®, Gattefossé, France).

Table 5. Reference formulations (capsules)

Formulation (mg/caps)	Ref. Formulation 1	Ref. Formulation 2	Ref. Formulation 3
Formula (I)	50.0	50.0	50.0
Labrafac® Lipophile	196.0	100.0	100.0
Labrafac® PG	102.0	-	-
Labrafil® M 1944 CS	-	135.0	46.0
Polysorbate 20	-	-	89.9
Kolliphor® RH 40	-	-	100.0
Kolliphor® HS 15	-	165.0	-
Gelucire® 44/14	95.0	-	-
TPGS	57.0	-	65.0
Transcutol®	-	50.0	50.0
Total	500.0	500.0	500.0

The assay measured the flux across simulated gastric and intestinal walls via UV spectroscopy (μDiss ProfilerTM, Pion Inc., Billerica, MA). Briefly, the assay was performed as follows. A vertical membrane flux cell consisting of a donor compartment and a receiver compartment, and separated by an Accurel PP 1E (55% porous, 100 μm thickness) polypropylene membrane (3M, Maplewood, MN) (FIG. 2), was impregnated with 50 μL of Pion GIT-0 lipid solution consisting of 20% w/w phospholipid dissolved into dodecane (Pion Inc., Billerica, MA) and attached to the receiver vessel. Both the donor and receiver compartments were agitated by magnetic stirring. The receiver compartment contained a plastic spacer and grating to elevate the stir bar above the membrane. Samples were introduced to the donor vessel by pre-weighing directly into the donor vessel and subsequently adding dissolution medium. Once the dissolution medium was added to the donor vessel, the receiver vessel was inserted into the donor vessel and suspended vertically 5 mm above the donor compartment by a plastic sleeve. For this assay, the simulated gastric (feed) media was 0.1 N HCl, pH 2 and included 200 μgA/mL of each SDD, and the simulated intestinal (receiver) media was 0.5 wt% SIF in PBS, pH 6.5 and included 100 μgA/mL of each SDD. The temperature for the assay was maintained at 44.5°C. UV probes (10 mm path length) connected to a Rainbow UV spectrometer (Pion Inc.) system were used to determine the apparent drug

concentration in the receiver vessels. Samples of the donor compartment were removed with a disposable pipet for centrifugation followed by HPLC and DLS analysis of the supernatant. The results are shown in FIG. 3 and Table 6, below.

Table 6. Non-sink dissolution data

Sample	C_{maxGB} (µg/mL)	$C_{max90\ IB}$ (µg/mL)	$AUC_{4\text{-}90IB}$ (min*µg/mL)	C_{90} (µg/mL)	$Ultra_{90}$ (µg/mL)	C_{1200} (µg/mL)
Formula (I)	0	1	10	0	0	3
1	6	80	6,800	80	79	90
2	17	74	6,240	73	73	86
4	6	4	200	4	5	36
5	23	55	3,180	55	54	83
6	35	71	6,070	71	77	83
Ref. Formulation 1	205	109	9,050	109	-	-
Ref. Formulation 2	249	120	10,160	120	-	-
Ref. Formulation 3	218	107	9,100	107	-	-

The membrane flux of 1 mg/mL gastric barrier/intestinal barrier (GB/IB) 0.5 wt% SIF doses of the compound of Formula (I) and spray-dried dispersions (2) 25% compound of Formula (I)/75% HPMCAS-L and (4) 25% compound of Formula (I)/75% PVP/VA 64 were also determined. The results are shown in FIG. 4 as receiver concentration vs. time and flux vs. time (smoothed derivative of receiver concentration x volume/surface area).

Example 2: Characterization of a spray-dried dispersion containing 25% of the compound of Formula (I) and 75% of a polyvinyl pyrrolidone vinyl acetate (PVP/VA) polymer

SDD stability screening

Several of the SDDs described in Example 1 were tested for chemical and physical stability. Wet SDD stability studies were performed, with samples stored at both 5°C and 25°C. Measurements were taken after 1 week and 2 weeks of storage. The results are shown in Table 7 below. The column with a retention time of 32.36 min correlates with the compound of Formula (I).

Table 7. Wet SDD stability data

Retention time (min)			11.04	16.79	17.26	30.94	32.26			
Relative retention time			0.34	0.52	0.53	0.96	1.00			
	Storage temp	**Timepoint**						**Total impurities**	**Potency (mgA/g)**	**Std Dev**
Ref. Std.						0.37	99.63	0.37		
Formula (I)						0.26	99.74	0.26		
Sample 1		initial		0.13	0.16	0.25	99.46	0.54	100	1.3
	5°C	1 week		0.03	0.03	0.26	99.69	0.31	99	0.0
		2 weeks		0.12	0.16	0.28	99.45	0.55	99	0.5
	25°C	1 week		0.03	0.04	0.26	99.67	0.33	99	0.3
		2 weeks		0.21	0.27	0.28	99.24	0.76	98	0.8
Sample 2		initial	<LOQ	0.07	0.08	0.26	99.59	0.41	247	0.3
	5°C	1 week	<LOQ	0.02	0.03	0.26	99.70	0.30	248	1.3
		2 weeks	<LOQ	0.22	0.27	0.27	99.24	0.76	246	0.3
	25°C	1 week	<LOQ	0.02	0.03	0.26	99.69	0.31	248	0.9
		2 weeks	<LOQ	0.23	0.28	0.26	99.23	0.77	246	1.4

LOQ = limit of quantification

Solution stability studies were also performed, with samples stored at both 5°C and 25°C. Measurements were taken after 1 week and 2 weeks of storage. The results are shown in Table 8 below. The column with a retention time of 32.36 min correlates with the compound of Formula (I).

Table 8. SDD solution stability data

Retention time (min)			31.51	32.26	
Relative retention time			0.97	1.00	
	Storage temp	**Timepoint**			**Total impurities**
Ref. Std.			0.74	99.26	0.74
Formula (I)			0.26	99.74	0.26
Sample 1		initial	0.33	99.67	0.33
	5°C	2 weeks	0.29	99.71	0.29
	25°C	2 weeks	0.38	99.62	0.38
Sample 2		initial	0.25	99.75	0.25
	5°C	2 weeks	0.26	99.74	0.26
	25°C	2 weeks	0.33	99.67	0.33

Stability studies were also performed for the SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64, with samples stored at both 5°C (closed with desiccant), 25°C (60% RH, closed with desiccant), and 30°C (65% RH, closed with desiccant). Measurements were taken after storage for 1 month, 2 months, 3 months, 6 months, and 12 months. No change in purity was observed after 12 months of storage. The results are shown in Table 9 below. The column with a retention time of 30.2 min correlates with the compound of Formula (I).

Table 9. SDD stability data

Retention time (min)			28.7	30.2		
Relative retention time			0.95	1.00		
	Storage conditions	**Timepoint**			**Total impurities**	**Potency (mgA/g)**
Crystalline Formula (I)			0.26	99.74	0.26	1001
Sample 4 (25% Formula (I):75% PVP/VA 64)		initial	0.26	99.74	0.26	245
	5°C (closed w/ desiccant)	1 month	0.25	99.75	0.25	247
		2 months	0.25	99.75	0.25	244
		3 months	0.26	99.74	0.26	246
		6 months	0.25	99.75	0.25	245
		12 months	0.25	99.75	0.25	248
	25°C/60% RH (closed with desiccant)	1 month	0.25	99.75	0.25	245
		2 months	0.25	99.75	0.25	247
		3 months	0.25	99.75	0.25	246
		6 months	0.25	99.75	0.25	242
		12 months	0.25	99.75	0.25	245
	30°C/65% RH (closed with desiccant)	1 month	0.25	99.75	0.25	249
		2 months	0.25	99.75	0.25	242
		3 months	0.25	99.75	0.25	246
		6 months	0.25	99.73	0.25	243
		12 months	0.25	99.75	0.25	242

While Samples 1 and 2 showed degradation after about 2 weeks of storage, the SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64 (Sample 4) was found to be both chemically and physically stable and was further screened and characterized as described below.

25% Formula (I)/75% PVP/VA 64 SDD process parameter screening manufacture Round 1

The 25% Formula (I)/75% PVP/VA 64 SDD was prepared on a Pharmaceutical Spray Dryer with 100 kg/hr drying gas capacity (PSD-1). The manufacturing summary is shown in Table 10, below.

Table 10. Manufacturing summary of process parameters

Formulation	25% Formula (I):75% PVP/VA 64
Solids Loading (wt%)	10
Batch Size (kg)	1.5
Solvent	Acetone
Atomizer (Pressure Swirl)	SK 80-16
Solution Flow-rate (g/min)	160
Atomization Pressure (psig)	480
Inlet Temperature (°C)	94
Outlet Temperature (°C)	40
Calculated Outlet Acetone Saturation (% RS)	6.2
Dry Yield (%)	73

Based on the 73% yield observed in the first round of process screening, three sprays were performed to investigate the effect of reducing solution throughput and outlet temperature on product yield. All sprays were conducted at a reduced flow-rate of 110 g/min. The outlet temperature was varied at 40°C (Lot A), 35°C (Lot B), and 30°C (Lot C). The outlet temperature was decreased while maintaining a low outlet acetone saturation to increase the difference between the chamber outlet temperature and the wet SDD T_g, thus improving product yields. The spray dryer chamber and outlet ductwork were cleaned between all manufactures. A manufacturing summary is shown in Table 11.

Table 11. Manufacturing summary for process parameters (1.5 kg batch size)

Description	Low Flow-Rate	Low Flow-Rate/Low Outlet Temperature	Low Flow-Rate/Lower Outlet Temperature
Lot	A	B	C
Solids Loading (wt%)	10	10	10
Batch Size (kg)	1.5	1.5	1.5
Solvent	Acetone	Acetone	Acetone
Atomizer (Pressure Swirl)	Steinen A75	Steinen A75	Steinen A75
Solution Flow-Rate (g/min)	110	110	110
Atomization Pressure (psig)	275	285	285
Inlet Temperature (°C)	79	72	63
Outlet Temperature (°C)	40	35	30
Calculated Outlet Acetone Saturation (% RS)	4.3	5.2	6.4
Calculated wet SDD T_g (°C)	72	71	69
Dry Yield (%)	55	80	43

The conditions used for Lot B were found to give the highest yield. One additional spray was then performed at the same processing conditions as Lot B while increasing the batch size from 1.5 kg to 3.5 kg to evaluate process consistency and to determine if product yield would continue to improve over time. The averaged process conditions for this lot are shown in Table 12.

Table 12. Manufacturing summary of process parameters (1.5 kg and 3.5 kg batch sizes)

Description	Low Flow-Rate/Low Outlet Temperature	Low Flow-Rate/Low Outlet Temperature/Larger Batch Size
Lot	B	D
Solids Loading (wt%)	10	10
Batch Size (kg)	1.5	3.5
Solvent	Acetone	Acetone
Atomizer (Pressure Swirl)	Steinen A75	Steinen A75
Solution Flow-Rate (g/min)	110	110
Atomization Pressure (psig)	285	285
Inlet Temperature (°C)	72	72
Outlet Temperature (°C)	35	35
Calculated Outlet Acetone Saturation (% RS)	5.2	5.2
Calculated wet SDD T_g (°C)	71	71
Dry Yield (%)	80	84

The 1.5 kg batch size (Lot D) was sprayed with an 84% yield compared to the 80% yield of the 3.5 kg batch (Lot B).

25% Formula (I)/75% PVP/VA 64 SDD process parameter screening characterization

The 25% Formula (I)/75% PVP/VA 64 SDDs manufactured to evaluate processing parameters were characterized for powder properties, performance, and physical and chemical properties. Testing included particle size distribution by Malvern, determination of bulk and tapped density, microcentrifuge dissolution, modulated differential scanning calorimetry (mDSC), powder x-ray diffraction (PXRD), scanning electron microscope (SEM), and assay and related substances. The results did not show any significant differences between the lots.

The particle size distribution (PSD) and tabulated powder properties data of the 25% Formula (I)/75% PVP/VA 64 SDDs are shown in Table 13. All 25% Formula (I)/75% PVP/VA 64 SDDs were observed to have a very similar PSD with a D_{50} of approximately 16 μm. All 25% Formula (I)/75% PVP/VA 64 SDDs were observed to have low bulk and tapped densities.

Table 13. Powder properties of process parameter screening PVP/VA-64 SDDs

Sample	Lot	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)	$D_{(3,2)}$ (µm)	$D_{(4,3)}$ (µm)	Span	Bulk density (g/mL)	Tapped density (g/mL)
40°C Outlet	A	5	15	34	8	17	1.93	0.12	0.25
35°C Outlet	B	5	16	36	9	19	1.97	0.11	0.23
30°C Outlet	C	5	15	32	7	17	1.86	0.12	0.27
35°C Outlet, 3.5 kg batch	D	5	16	38	9	19	1.98	0.12	0.24

The 3.5 kg batch size lot was analyzed and compared to process parameter Lot A. Dissolution performance was similar for each of these lots. Dissolution was rapid to C_{max} and high free drug was sustained through 90 minutes. These data are shown in Table 14.

Table 14. Dissolution performance of Lot A (1.5 kg batch size) vs. Lot D (3.5 kg batch size)

Sample	C_{max90} (µg/mL)	AUC_{90} (min*µg/mL)	C_{90} (µg/mL)	$Ultra_{90}$ (µg/mL)
Lot A	447	37,740	437	319
Lot D	437	37,120	433	301

The 25% Formula (I)/75% PVP/VA 64 SDDs were also evaluated by DSC, PXRD, and SEM. The DSC thermograms showed a single T_g at 84°C, indicating homogeneous dispersions. PXRD diffractograms showed no evidence of crystals in the SDDs. SEM images showed inflated sphere morphology with some broken particles and some very small particles.

Additional testing on Lot B was carried out, which included assessing the chemical/physical stability of both spray solution and SDD prior to secondary drying (wet

SDD) to establish maximum in-process hold times. Residual acetone concentration as a function of secondary drying time in a convection tray dryer was also evaluated to nominate tray drying conditions to ensure the SDD is dried below International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for acetone.

Residual acetone content as a function of drying time was assessed by drying wet SDD in a tray dryer and collecting samples over a 24-hour period. Wet SDD was dried at 40°C/15% relative humidity (RH) and was observed to dry below ICH acetone guidelines (0.5 wt%, 5000 ppm) by four hours.

Spray solution hold time was determined by making up a representative solution that contained 2.5 wt% compound of Formula (I), 7.5 wt% PVP/VA 64, and 90 wt% acetone. These solutions were analyzed initially for related substances. and then aged at 5°C and 25°C. Aliquots were taken and analyzed for related substances periodically for 14 days. Results showed no change in impurity profile at either condition through 14 days.

Wet SDD was analyzed for impurities after storage at 5°C and 25°C for 1 and 2 weeks and compared to the impurity profiles of the ingoing compound of Formula (I) and the SDD that was secondarily dried immediately after spray drying. The impurity profiles were similar to that of the initial dried sample and the ingoing compound of Formula (I) through 2 weeks of storage.

The wet SDD stability samples were characterized for physical stability by DSC, PXRD, and SEM. DSC thermograms showed a single T_g at 81°C, indicative of a homogeneous dispersion with no phase separation. The PXRD diffractograms did not show any evidence of crystals after storage at either condition. SEM images showed a typical morphology of mostly inflated spheres with some broken particles.

Example 3: Preparation of a 1000 g batch of a spray-dried dispersion containing 25% of the compound of Formula (I) and 75% PVP/VA 64

A 1000 g batch of the spray-dried dispersion containing 25% of the compound of Formula (I) and 75% PVP/VA 64 was prepared as described in Example 2 for the 1.5 kg and 3.5 kg batches. Briefly, acetone (90% (w/w) of the total mixture) was added to the mixing tank followed by the addition of 250.0 g of the compound of Formula (I) (2.5% (w/w) of the total mixture). The mixture was mixed for 30 minutes in the dark at a temperature range of 15°C to 27°C. At the end of the mixing period, the solution was clear and free of undissolved solids.

The PVP/VA 64 (750.0 g, 7.5% (w/w) of the total mixture) was then added and the mixture was stirred for an additional 30 minutes in the dark at a temperature range of 15°C to 27°C. At the end of the mixing period, the solution was clear and free of undissolved solids.

The solution was pumped and atomized in a drying chamber. The spray-dried dispersions were prepared in a Pharmaceutical Spray Dryer with 100 kg/hr drying gas capacity (PSD-1). The inlet temperature was set at 75°C (varied between 60°C-90°C). The outlet temperature was set at 35°C (varied between 32°C-38°C). The feed pressure was set at 280 psig (varied between 230-330 psig). The feed rate was set at 110 g/min (varied between 90-130 g/min). The spray dried powder was then dried in a convection tray dryer with a bed depth of ≤ 2.5 cm at 40°C (±5°C) and 15% relative humidity (±10%) for 24 hours under amber light. The residual acetone after drying was < 0.5 wt% (5000 ppm). FIG. 5 is a flow diagram of the manufacturing process.

Example 4: Preparation of spray-dried dispersion formulations of the compound of Formula (I) for clinical use

The spray-dried dispersion (SDD) containing 25% compound of Formula (I) and 75% PVP/VA 64, prepared as described above, was formulated as a suspension or a capsule for clinical use.

Suspension preparation

A suspension that contained 50 mg of the SDD was prepared as follows. A 30 mL amber dosing bottle was tared on a balance. 200.0 mg SDD (50 mgA) ± 5% was then weighed into the dosing bottle. Using a 10-mL syringe, 5.0 mL of water (purified, USP) was added to the dosing bottle and the bottle was capped and shaken moderately for 30 seconds. The SDD suspension was stored in an amber vial at 2-8°C prior to use, and dosed within 24 hours of preparation.

Capsule preparation

An empty hard gelatin capsule, size 0 (Capsugel, Morristown, NJ), was placed on a balance and the weight was recorded. 200.0 mg SDD (50 mgA) ± 5% was then weighed onto weigh paper or an equivalent. All contents were transferred to the capsule using a ProFunnel device for Size 0 capsules. The filled capsule was placed on the balance and the weight was recorded. The weight of the empty capsule was subtracted from the filled weight, ensuring that the weight of the SDD within the capsule was 200.0 mg SDD ± 5%, or from 190.0 mg to 210.0 mg. The capsule was securely closed with the head, assuring it clicked into place. The capsules

were stored in an amber vial at 2-8°C prior to use, and were dosed within 24 hours of preparation.

Example 5: Dog relative bioavailability and food effect study

Four spray-dried dispersions (SDDs), formulated in 0.25% methylcellulose as a suspension, were prepared: (1) 25% compound of Formula (I)/75% HPMCAS-L; (2) 10% compound of Formula (I)/90% HPMCAS-L; (3) 25% compound of Formula (I)/75% methyl methacrylate copolymer (1:1) (Eudragit® L100); and (4) 25% compound of Formula (I)/75% PVP/VA 64. A clinical capsule formulation was prepared as a reference formulation (Reference Formulation 1 from Table 5, above).

Dogs (two cohorts, six dogs in each) were dosed in six sessions, including fasted state sessions and fed sessions (high fat diet), with 50 mg dose of one of the SDDs or reference per dog in a 3-way crossover design. Each session had a 3-day washout in between. All formulations were well tolerated. The study design is shown in Table 15, below.

Table 15. Study design

Cohort 1	**Session 1 (Fasted)**	**Session 2 (Fed)**	**Session 3 (Fasted)**	**Session 4 (Fed)**	**Session 5 (Fasted)**	**Session 6 (Fed)**
Dog 1001	Reference	Reference	SDD 1	SDD 1	SDD 2	SDD 2
Dog 1002	Reference	Reference	SDD 1	SDD 1	SDD 2	SDD 2
Dog 2001	SDD 1	SDD 1	SDD 2	SDD 2	Reference	Reference
Dog 2002	SDD 1	SDD 1	SDD 2	SDD 2	Reference	Reference
Dog 3001	SDD 2	SDD 2	Reference	Reference	SDD 1	SDD 1
Dog 3002	SDD 2	SDD 2	Reference	Reference	SDD 1	SDD 1
Cohort 2	**Session 1 (Fasted)**	**Session 2 (Fed)**	**Session 3 (Fasted)**	**Session 4 (Fed)**	**Session 5 (Fasted)**	**Session 6 (Fed)**
Dog 4001	Reference	Reference	SDD 3	SDD 3	SDD 4	SDD 4
Dog 4002	Reference	Reference	SDD 3	SDD 3	SDD 4	SDD 4
Dog 5001	SDD 3	SDD 3	SDD 4	SDD 4	Reference	Reference
Dog 5002	SDD 3	SDD 3	SDD 4	SDD 4	Reference	Reference
Dog 6001	SDD 4	SDD 4	Reference	Reference	SDD 3	SDD 3
Dog 6002	SDD 4	SDD 4	Reference	Reference	SDD 3	SDD 3

The area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), the apparent terminal half-life ($t_{½}$), and the time to achieve maximum plasma concentration (t_{max}) were calculated. Results are shown in Table 16, below, and in FIGS. 6A and 6B.

Table 16. Pharmacokinetic results

Cohort	Form	Fasted [Mean (%CV)]		Fed [Mean (%CV)]		Ratio of Fed/Fasted [Mean (%CV)]	
		C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	C_{max}	AUC
1 (N=4)*	Ref	652 (55.5)	5170 (69.4)	3650 (19.5)	20100 (22)	6.9 (48)	5.5 (69.2)
	SDD 1	524 (62.7)	2870 (62.9)	5760 (25.6)	22800 (14.6)	15.4 (66.9)	8 (89.6)
	SDD 2	487 (45.7)	3950 (26.4)	4220 (27.4)	18100 (26.8)	16.5 (40.7)	6.3 (34.6)
2 (N=6)	Ref	854 (40.2)	5520 (59.1)	4220 (27.4)	18100 (26.8)	5.8 (46.5)	4.1 (49.2)
	SDD 3	453 (28.3)	2830 (21.6)	5320 (13.5)	23800 (26.1)	12.6 (30.3)	8.6 (22.2)
	SDD 4	353 (20.1)	1840 (21.9)	3060 (20.7)	17200 (20.5)	8.9 (29.3)	8.4 (46.1)

*Animals 2001 and 2002 were excluded from summary statistics due to emesis in all 3 fed sessions, which resulted in notably lower exposures

The results showed that $t_{1/2}$ and t_{max} were similar among the formulations, and comparable between the fed and fasted states. Under the fed state with a high fat meal, exposures increased and inter-animal variability decreased. The food effect was more notable with the spray-dried dispersion formulations, especially for peak exposure (C_{max}).

Compared to the reference form, SDD 4 (25% compound of Formula (I)/75% PVP/VA 64) appeared to have lower inter-animal variability, lower exposures under the fasted state, and slightly lower C_{max} but relatively comparable AUC in the fed state.

Example 6: Phase 1 study to evaluate the pharmacokinetics, effect of food on pharmacokinetics, and safety of the compound of Formula (I) in healthy adult subjects

The present study was designed to evaluate the pharmacokinetics (PK) of the compound of Formula (I) as well as to evaluate the effect of a fed condition on the PK of the compound of Formula (I). The 50 mg dose was chosen for this study because it was within the tested dose range in completed Phase 1 and Phase 2 trials and was well tolerated in those studies. The objectives of the study were: to evaluate the PK of the compound of Formula (I) 50 mg in healthy adult subjects; to evaluate the effect of food on the PK of the compound of Formula (I) 50 mg; and to evaluate the safety and tolerability of the compound of Formula (I) 50 mg.

Study Design

This was a Phase 1, open-label, randomized, 2-period crossover study of the PK and the effect of food on the PK of the compound of Formula (I) in 16 healthy male and female adult subjects, 18 to 55 years of age.

After providing informed consent, subjects were screened for eligibility to participate in the study up to 28 days prior to Day 1 of treatment period 1. Eligible subjects were admitted to the clinical unit on Day -1 and randomized to 1 of the 2 treatment sequences (16 subjects [8 males and 8 females]; see Table 17, below). On Day 1 of each treatment period, subjects received a single dose of the compound of Formula (I) 50 mg under fasted or fed conditions. There were 21 days between doses.

Table 17. Treatment sequences

Treatment sequence	Treatment period 1	Treatment period 2
1	Formula (I) – fasted	Formula (I) – fed
2	Formula (I) – fed	Formula (I) – fasted

Subjects were required to fast for at least 4 hours before check-in on Day -1. In the fasted condition, subjects were required to fast overnight for at least 10 hours prior to dosing and continued to fast for an additional 4 hours after dosing. In the fed condition, subjects were required to fast overnight for at least 10 hours and then ingest a liquid dietary supplement with study drug (liquid dietary supplement was consumed within 30 minutes) and not consume any other food for 4 hours after dosing. During both treatment periods, water was not permitted for

1 hour before dosing until 2 hours after dosing except for the water/liquid dietary supplement provided for study drug dosing. Vanilla-flavored Ensure Plus® was used as the liquid dietary supplement.

On Day 1 of each treatment period, subjects were dosed with the compound of Formula (I) 50 mg. Blood samples were collected for PK analysis over a period of 36 hours during the in-house stay. Subjects remained in the unit on the day of dosing and were discharged on Day 2 of each treatment period, following completion of all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects returned to the clinical unit on an outpatient basis for PK blood sample collection and safety assessments. On Day 21 of treatment period 1, subjects arrived at the site and had Day 21 assessments completed in the evening, and they stayed overnight at the site and began Day 1 of treatment period 2 the following day. A final follow-up study visit was conducted on Day 22 of treatment period 2 (21 ± 2 days after treatment period 2 dosing) or upon early termination.

During each treatment period, blood samples for PK analysis were collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

Safety assessments (including clinical safety laboratory tests, vital sign measurements, physical examinations, and electrocardiograms (ECGs)) were conducted at scheduled times throughout the study. Adverse events (AEs) and the use of concomitant medications were monitored throughout the study. FIG. 7 illustrates the study design.

Test product, dose and mode of administration

The compound of Formula (I) was supplied as an encapsulated, lipidic semi-solid containing 50 mg of the compound of Formula (I) as free base equivalent for oral administration. Subjects swallowed a single capsule with approximately 240 mL of water in the fasted condition. Subjects swallowed a single capsule with a liquid dietary supplement (Ensure Plus® [237 mL container]) with up to an additional 120 mL of water in the fed condition.

Duration of treatment

The duration of study participation for each adult subject was approximately 10 weeks, including up to 28 days of screening, 2 days of dosing separated by 21 days, and a final follow-up study visit 21 days after receiving the last dose of study drug during treatment period 2.

Criteria for Evaluation

Pharmacokinetics

The following plasma PK parameters were calculated for the compound of Formula (I):

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-tlast}}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours ($AUC_{0\text{-}24}$)
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)
- Molar AUC ratio of the hydroxylated metabolite of the compound of Formula (I) to the parent drug the compound of Formula (I)

The following plasma PK parameters were calculated only for the compound of Formula (I):

- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

Safety

Safety was monitored throughout the study and included the following assessments:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiograms (ECGs)

Statistical Methods

Pharmacokinetic parameters were calculated using noncompartmental methods and summarized by condition (fed or fasted) using descriptive statistics. Two-sided 90% confidence intervals were calculated for the ratio under the fed condition vs. under the fasted condition for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} for the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I).

Safety data were summarized with descriptive statistics.

Pharmacokinetics

Pharmacokinetic assessments

PK plasma samples for analyses of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) were collected at the following times during each treatment period:

- Day 1: within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5,6, 7, 8, 9, 10, 12, and 16 hours after dosing.
- Day 2: approximately 24 and 36 hours after dosing.
- Day 8: approximately 168 hours after dosing.
- Day 15: approximately 336 hours after dosing.
- Approximately 504 hours after dosing (for treatment period 1, this sample was collected in the morning at least 30 minutes prior to the predose sample on Day 1 of treatment period 2).
- Final study visit for subjects who terminate early: 1 sample.

Blood samples on Day 1 were collected within 5 minutes of the scheduled sampling times (other than the predose sample). Blood samples on Days 2, 8, and 15 were collected within 2 hours of the scheduled sampling time. The 504 hour blood sample for treatment period 2 had a ± 2-day window. A PK sample was to be collected from subjects who terminated early. The exact time of sampling in hour and minutes was recorded.

Bioanalytical methods

Plasma samples were analyzed for the compound of Formula (I) and for its hydroxylated metabolite by inVentiv Health, Princeton NJ, in compliance with Good Laboratory Practice (GLP) and relevant Standard Operating Procedures (SOPs).

The concentrations of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) were quantified in plasma samples according to validated

methods using tandem mass spectrometry in positive ion mode. This method was validated for the analysis of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) in 25.0 µL dipotassium ethylenediaminetetraacetic acid (K_2-EDTA) human plasma samples over concentration ranges of 5.00 to 2500 ng/mL and 0.500 and 250 ng/mL, respectively. All analytical results were within acceptable limits. Incurred sample reanalysis (ISR) was successfully conducted in this study for both analytes.

Results

Pharmacokinetic results

Eight male and eight female subjects were enrolled. The mean age was 37.1 years (range, 21 to 55 years). The majority of subjects were White (93.8%) and of Hispanic ethnicity (81.3%). The mean weight at screening was 160.28 lbs (range, 102.0 to 222.2 lbs) and mean BMI was 25.50 kg/m^2 (range, 20.7 to 30.5 kg/m^2). The randomization was well balanced with respect to demographics and baseline characteristics.

All 16 subjects were included in the safety analysis set. No subjects were excluded from the safety analysis set and no subject had his or her PK data excluded from analysis.

The mean plasma concentration versus time profiles for the compound of Formula (I) under fasted and fed conditions are presented in FIGS. 8A and 8B, respectively. The compound of Formula (I) was slowly absorbed after oral administration in both fasted and fed conditions. Mean plasma concentrations were lower in the fasted than in the fed condition.

PK parameters for the compound of Formula (I) after treatment with the compound of Formula (I) under fasted and fed conditions are summarized in Table 18, below, where AUC_{0-24}=area under the plasma concentration vs. time curve from 0 to 24 hours, $AUC_{0\text{-}tlast}$=AUC from 0 hours to last measurable concentration, $AUC_{0-\infty}$=AUC from 0 hours extrapolated to infinity, CL/F=apparent systemic clearance after oral administration, CV=coefficient of variation, C_{max}=maximum plasma concentration, CV(%)=coefficient of variation, max=maximum, min=minimum, MRT=apparent mean residence time, PK=pharmacokinetic, SD=standard deviation, $t_{½}$=apparent terminal half-life, T_{lag}=delay time between time of dosing and time of appearance of measurable test article, t_{max}=time to maximum plasma concentration, VZ/F=apparent volume of distribution during the terminal phase after oral administration.

The PK data for t_{max}, T_{lag}, $t_{½}$, MRT, and Vz/F were rounded to 2 significant figures and all other parameters ($AUC_{0\text{-}24}$, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, C_{max}, and CL/F) were rounded to 3

significant figures. The last significant figure was rounded up if the digit to the right of it was ≥5, and was rounded down if the digit to the right of it was ≤4.

Table 18. Summary of Formula (I) PK parameters (safety analysis set)

Parameter Statistic	Fasted Formula (I) (50 mg) (N=16)	Fed Formula (I) (50 mg) (N=15)
AUC_{0-24} (ng×hr/mL)		
Mean (SD)	5590 (2230)	9950 (2540)
Geometric CV%	32.7	26.2
$AUC_{0-tlast}$ (ng×hr/mL)		
Mean (SD)	8020 (5110)	16200 (5450)
Geometric CV%	53.6	39.7
$AUC_{0-\infty}$ (ng×hr/mL)		
Mean (SD)	9440 (2990) [n=7]	17800 (4990) [n=12]
Geometric CV%	39.7	28.1
C_{max} (ng/mL)		
Mean (SD)	731 (301)	1550 (392)
Geometric CV%	36.6	24.2
t_{max} (hours)		
Median (min, max)	6.0 (3.0, 6.0)	5.0 (3.0, 6.0)
T_{lag} (hours)		
Mean (SD)	0.63 (0.22)	0.94 (0.37)
$t_{½}$ (hours)		
Mean (SD)	33 (17) [n=7]	42 (6.8) [n=12]
Geometric CV%	99	15
MRT (hours)		
Mean (SD)	28 (11) [n=7]	30 (5.0) [n=12]
Geometric CV%	49	16
CL/F (L/hr)		
Mean (SD)	6.0 (2.7) [n=7]	3.0 (0.82) [n=12]
Geometric CV%	40	28
VZ/F (L)		
Mean (SD)	240 (120) [n=7]	180 (57) [n=12]
Geometric CV%	67	30

As seen in Table 18, above, administration of the compound of Formula (I) 50 mg under fed compared with fasted conditions resulted in a higher mean C_{max} of the compound of Formula (I) (approximately 2-fold higher; 1550 vs. 731 ng/mL), a longer $t_{½}$ (42 vs. 33 hours), a slightly shorter median t_{max} (5.0 vs. 6.0 hours), and a higher mean $AUC_{0-\infty}$ (approximately 2-fold higher; 17800 vs. 9440 ng×hr/mL). The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0-tlast}$ for fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when

administered with food. The upper and lower 90% confidence interval (CI) bounds for both C_{max} (187.4% and 255.1%, respectively) and $AUC_{0\text{-tlast}}$ (182.9% and 253.1%, respectively) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure.

Frequency distribution of T_{lag} and t_{max} values are presented in Table 19 and Table 20, respectively. Spaghetti plots for the compound of Formula (I) $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} are shown in FIGS. 9A, 9B, and 9C, respectively.

Table 19. Frequency distribution of plasma Formula (I) T_{lag} values by treatment (safety analysis set)

T_{lag} (hr)	**Statistic**	**Fasted (Formula (I) 50 mg) (N=16)**	**Fed (Formula (I) 50 mg) (N=15)**
0.50	n (%)	11 (68.8%)	3 (20.0%)
0.53	n (%)	1 (6.3%)	0 (0.0%)
0.55	n (%)	0 (0.0%)	1 (6.7%)
1.00	n (%)	4 (25.0%)	8 (53.3%)
1.02	n (%)	0 (0.0%)	1 (6.7%)
1.03	n (%)	0 (0.0%)	1 (6.7%)
2.00	n (%)	0 (0.0%)	1 (6.7%)

Table 20. Frequency distribution of plasma Formula (I) T_{max} values by treatment (safety analysis set)

T_{max} (hr)	Statistic	Fasted (Formula (I) 50 mg) (N=16)	Fed (Formula (I) 50 mg) (N=15)
3.00	n (%)	1 (6.3%)	2 (13.3%)
4.02	n (%)	1 (6.3%)	0 (0.0%)
5.00	n (%)	4 (25.0%)	8 (53.3%)
5.03	n (%)	0 (0.0%)	1 (6.7%)
5.05	n (%)	0 (0.0%)	1 (6.7%)
6.00	n (%)	10 (62.5%)	2 (13.3%)
6.02	n (%)	0 (0.0%)	1 (6.7%)

The compound of Formula (I) was slowly absorbed after oral administration in the fasted and fed conditions. In the fasted condition, the mean compound of Formula (I) C_{max} was approximately 53% lower than in the fed condition (731 vs. 1550 ng/mL). Due to a prolonged elimination phase, $t_{½}$ values and therefore, $AUC_{0-\infty}$ values could not be determined for some the compound of Formula (I) concentration-time profiles. Mean $AUC_{0-\infty}$ was approximately 47% lower in the fasted condition than in the fed condition (9440 vs. 17800 ng×hr/mL) for those subjects for whom $AUC_{0-\infty}$ could be determined. Mean $AUC_{0-tlast}$ was approximately 50% lower in the fasted condition than in the fed condition (8020 vs. 16200 ng×hr/mL). Median t_{max} was slightly longer in the fasted condition than in the fed condition (6.0 vs. 5.0 hours) and mean $t_{½}$ was shorter in the fasted condition than in the fed condition (33 vs. 42 hours) for those subjects for whom a $t_{½}$ could be determined. Variability in the compound of Formula (I) PK (geometric CV%) for AUC, C_{max}, $t_{½}$, and MRT was lower in the fed condition compared with the fasted condition.

The geometric mean ratios and associated 90% CIs for $AUC_{0-tlast}$ and C_{max} for the compound of Formula (I) after treatment with the compound of Formula (I) for the fed vs. fasted condition are provided in Table 21, below, where $AUC_{0-tlast}$= AUC from 0 hours to last measurable concentration, C_{max}=maximum plasma concentration, and PK=pharmacokinetic.

Table 21. Formula (I) geometric mean ratios for PK exposure parameters under fed vs. fasted conditions (safety analysis set)

Parameter	Ratio[a] (%) (Fed vs. Fasted Condition)	90% Confidence Interval[b]
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	215.2	182.9, 253.1
C_{max} (ng/mL)	218.6	187.4, 255.1

[a] Ratio of geometric least-squares means was based on a mixed model using log-transformed (base 10) data.

[b] The 90% confidence interval for geometric mean ratio was based on least-squares means using log-transformed (base 10) data.

The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0\text{-tlast}}$ for the fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when administered with food. The upper and lower 90% CI bounds for both C_{max} (187.4%, 255.1%) and $AUC_{0\text{-tlast}}$ (182.9%, 253.1%) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure. Due to the missing $AUC_{0-\infty}$ values, the food effect on overall exposure was not assessed using $AUC_{0\text{-}\infty}$ values.

Conclusion

Administration of the compound of Formula (I) 50 mg under fed compared with fasted conditions resulted in a higher mean C_{max} of the compound of Formula (I) (approximately 2-fold higher; 1550 vs. 731 ng/mL), a longer $t_{½}$ (42 vs. 33 hours), a slightly shorter median t_{max} (5.0 vs. 6.0 hours), and a higher mean $AUC_{0\text{-}\infty}$ (approximately 2-fold higher; 17800 vs. 9440 ng×hr/mL). The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0\text{-tlast}}$ for fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when administered with food. The upper and lower 90% CI bounds for both C_{max} (187.4%, 255.1%) and $AUC_{0\text{-tlast}}$ (182.9%, 253.1%) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure. Similar results were observed with the hydroxylated metabolite of the compound of Formula (I). Overall, these results indicate that the compound of Formula (I) 50 mg was well tolerated in healthy subjects when administered under fasted or fed conditions and that the total AUC and C_{max} were increased when the compound of Formula (I) was taken with food.

Example 7: Phase 1 study to evaluate the relative bioavailability, effect of food on pharmacokinetics, and safety of formulations of the compound of Formula (I) in healthy adult subjects

A Phase 1 study to compare the relative bioavailability of a 50 mg dose of different formulations of the compound of Formula (I) as well as to evaluate the effect of fasting and fed conditions on the pharmacokinetics (PK) of the compound of Formula (I) was designed. The 50 mg dose was chosen for this study because it is within the tested dose range in completed Phase 1 and Phase 2 trials and was well tolerated in those studies. The objectives of the study are: to evaluate the PK and compare the relative bioavailability of the compound of Formula (I) 50 mg formulations in healthy adult subjects; to evaluate the effect of food on the PK of the compound of Formula (I) 50 mg formulations; and to evaluate the safety and tolerability of the compound of Formula (I) 50 mg formulations.

Study Design

This is a Phase 1, open-label, randomized, three-period crossover study of the relative bioavailability and the effect of food on the PK of the compound of Formula (I) 50 mg in healthy adult subjects. During treatment period 1 and treatment period 2, subjects will receive a single dose of the compound of Formula (I) 50 mg administered as an encapsulated, lipidic semi-solid (reference) and 1 of 2 different spray-dried dispersion (SDD) test formulations (suspension or capsule) under fed conditions, and during treatment period, three subjects will receive the same SDD test formulation under fasted conditions.

A total of 36 healthy adult subjects will be randomized to 1 of 4 treatment sequences (9 subjects per sequence; approximately equal distribution of males and females per sequence; see Table 22, below). There will be 21 days between each dose.

Table 22. Treatment sequences

Treatment sequence	Treatment period 1 (Fed)	Treatment period 2 (Fed)	Treatment period 3 (Fasted)
1	Reference	SDD suspension	SDD suspension
2	SDD suspension	Reference	SDD suspension
3	Reference	SDD capsule	SDD capsule
4	SDD capsule	Reference	SDD capsule

After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days prior to Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1, and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During treatment periods 1 and 2, subjects will fast overnight for at least 10 hours and then ingest a liquid dietary supplement (vanilla-flavored Ensure Plus®, 237 mL container) with the study drug and not consume any other food for 4 hours after dosing. During treatment period 3, subjects will fast overnight for at least 10 hours prior to dosing and continue to fast for an additional 4 hours after dosing. During all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water/liquid dietary supplement provided for study drug dosing.

On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 50 mg and have blood samples collected for PK analysis. Subjects will complete a taste satisfaction questionnaire after study drug ingestion on Day 1 of treatment period 3 (only for subjects who receive the SDD suspension under the fasted condition). Subjects will remain in the unit on the day of dosing and will be discharged on Day 2 of each treatment period, following completion of all required procedures, including collection of the 36-hour PK sample. On the mornings of Days 8 and 15 of each treatment period, subjects will return to the clinical unit on an outpatient basis for PK blood sample collection and safety assessments. On Day 21 of treatment period 1 and treatment period 2, subjects will arrive at the site and have Day 21 assessments completed, and they will stay overnight at the site and begin Day 1 of treatment period 2 or treatment period 3 the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 3 (21 ± 2 days after treatment period 3 dosing) or upon early termination.

Blood samples for PK analysis and safety assessments will be collected/conducted at scheduled times throughout the study. The study design schematic is shown in FIG. 10.

Duration of treatment

The expected duration of study participation for each healthy adult subject will be approximately 13 weeks, including up to 28 days of screening, 3 doses each separated by 21 days, and a final follow-up study visit 21 days after receiving the last dose of study drug during treatment period 3.

Test product, dose, and mode of administration

The compound of Formula (I) will be supplied as two different test formulations for oral administration: as powder in bottles for constitution into a suspension (20 mL) and as

powder-filled capsules. The compound of Formula (I) test formulations will contain 50 mg of the compound of Formula (I) as free base equivalent. Subjects must swallow the study drug with a liquid dietary supplement (Ensure Plus® [237 mL container]) with an additional 100 mL of water (SDD capsule formulation) or with an additional 80 mL of water (SDD suspension formulation) during treatment period 1 or 2. Subjects must swallow the study drug with 330 mL of water (SDD capsule formulation) or 310 mL of water (SDD suspension formulation) during treatment period 3.

Reference therapy, dose, and mode of administration

The compound of Formula (I) reference formulation (encapsulated, lipidic semi-solid formulation) will be supplied as capsules for oral administration. The compound of Formula (I) reference capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. Subjects must swallow a single capsule with a liquid dietary supplement (Ensure Plus [237 mL container]) with an additional 100 mL of water during treatment period 1 or 2.

Criteria for Evaluation

Pharmacokinetics

Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to the time of the last measurable concentration ($AUC_{0\text{-}tlast}$)
- Area under the plasma concentration curve extrapolated from 0 hours to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)

- Molar AUC ratio of primary metabolite(s) to the parent drug the compound of Formula (I)

The following plasma PK parameters will be calculated only for the compound of Formula (I):

- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

Other assessment

A taste satisfaction questionnaire will be administered.

Safety assessments

Safety will be monitored throughout the study and will include the following assessments:

- AEs
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiogram (ECG)

Statistical methods

Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by formulation using descriptive statistics. Two-sided 90% confidence intervals will be calculated for the ratio of each test formulation (SDD suspension and SDD capsule) vs. the reference formulation for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} for the compound of Formula (I) and metabolites under fed conditions. Further, two-sided 90% confidence intervals will be calculated for the ratio of each test formulation under fasted conditions vs. under fed conditions for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} for the compound of Formula (I) and metabolites.

Safety and taste satisfaction questionnaire data will be summarized with descriptive statistics.

Results

Pharmacokinetic results

Pharmacokinetic results are shown in Tables 23-26, below.

Table 23: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set – SDD Suspension Group)

		Compound of Formula (I) Plasma Concentration	
Parameter (units) Statistic	**Reference Capsule (Fed) (N=18)**	**SDD Suspension (Fed) (N=18)**	**SDD Suspension (Fasted) (N=18)**
$AUC_{0\text{-}tlast}$ (ng×hr/mL)			
Mean (SD)	16600 (7880)	5980 (3960)	737 (417)
Geom CV(%)	46.8	72.8	68.7
$AUC_{0\text{-}\infty}$ (ng×hr/mL)			
Mean	17400 (8010)	6500 (4180)	893 (480)
Geom CV(%)	45.4	71.7	60.1
C_{max} (ng/mL)			
Mean (SD)	1480 (506)	672 (323)	72.3 (44.9)
Geom CV(%)	32.1	57.9	57.5
t_{max} (hr)			
Median (min,max)	5.0 (3.0, 6.0)	5.0 (5.0, 10)	7.0 (5.0, 12)
T_{lag} (hr)			
Mean (SD)	1.0 (0.31)	0.85 (0.29)	1.2 (0.65)
$t_{½}$ (hr)			
Mean (SD)	50 (20)	19 (6.1)	9.0 (0.46)
Geom CV(%)	140	93	23
MRT (hr)			
Mean (SD)	36 (43)	23 (24)	17 (2.9)
Geom CV(%)	84	62	18
CL/F (L/hr)			
Mean (SD)	3.4 (1.4)	11 (8.0)	80 (54)
Geom CV(%)	45	72	63
Vz/F (L)			
Mean (SD)	180 (260)	210 (140)	970 (560)
Geom CV(%)	93	77	53
T_{last} (hr)			

Mean (SD)	170 (140)	77 (110)	31 (7.6)
Geom CV(%)	120	92	30

Table 24: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set – SDD Suspension Group)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	32.2	(26.4%, 39.4%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	33.5	(27.7%, 40.6%)
C_{max} (ng/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	42.2	(34.8%, 51.2%)
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	4.4	(3.4%, 5.7%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	5.0	(3.8%, 6.5%)
C_{max} (ng/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	4.5	(3.8%, 5.4%)

Table 25: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set – SDD Capsule Group)

		Compound of Formula (I) Plasma Concentration	
Parameter (units) Statistic	**Reference Capsule (Fed) (N=18)**	**SDD Capsule (Fed) (N=18)**	**SDD Capsule (Fasted) (N=17)**
$AUC_{0\text{-tlast}}$ (ng×hr/mL)			
Mean (SD)	19500 (7960)	9470 (4670)	1840 (1650)
Geom CV(%)	50.4	48.0	78.7
$AUC_{0\text{-}\infty}$ (ng×hr/mL)			
Mean	20100 (7850)	10000 (4610)	2120 (1830)
Geom CV(%)	47.1	44.9	73.7
C_{max} (ng/mL)			
Mean (SD)	1770 (494)	1110 (449)	143 (110)

Geom CV(%)	25.7	44.5	74.1
t_{max} (hr)			
Median (min,max)	5.0 (5.0, 8.0)	5.0 (3.0, 6.0)	7.0 (6.0, 12)
T_{lag} (hr)			
Mean (SD)	1.0 (0.38)	1.3 (0.49)	1.2 (0.88)
$t_{½}$ (hr)			
Mean (SD)	35 (18)	26 (20)	14 (11)
Geom CV(%)	69	98	49
MRT (hr)			
Mean (SD)	28 (12)	25 (14)	21 (9.2)
Geom CV(%)	45	55	31
CL/F (L/hr)			
Mean (SD)	3.0 (1.5)	5.9 (2.4)	36 (18)
Geom CV(%)	47	45	74
Vz/F (L)			
Mean (SD)	130 (61)	190 (140)	630 (380)
Geom CV(%)	47	75	72
T_{fast} (hr)			
Mean (SD)	170 (96)	100 (89)	44 (32)
Geom CV(%)	91	100	39

Table 26: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set – SDD Suspension Group)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	48.2	(41.4%, 56.1%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	49.7	(43.1%, 57.2%)
C_{max} (ng/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	59.8	(51.7%, 69.2%)
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	8.0	(5.7%, 11.2%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	9.0	(6.6%, 12.4%)
C_{max} (ng/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	6.7	(4.9%, 9.2%)

Example 8: Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia

A Phase 2 study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of the compound of Formula (I) in adult subjects with classic congenital adrenal hyperplasia (CAH) was designed. The objectives of the study are: to assess the safety and tolerability of two ascending doses of the compound of Formula (I) in adult subjects with CAH; to evaluate the effect of repeated doses of the compound of Formula (I) on endogenous levels of PD biomarkers in adult subjects with CAH; and to evaluate plasma exposures following repeated doses of the compound of Formula (I) administered nightly.

The lower dose strength selected for this study, the compound of Formula (I) 50 mg, was well tolerated in both single and repeat-dose safety and PK studies in healthy volunteers. Doses up to 100 mg were also well tolerated in both single-dose and repeat-dose Phase 1 studies in healthy volunteers, and importantly, in a large Phase 2 study in non-elderly female and male subjects with major depressive disorder receiving the compound of Formula (I) during an 8-week, double-blind treatment period. Furthermore, the anticipated steady state exposures with the selected the compound of Formula (I) doses, using the predicted C_{max} and AUC, are within the acceptable safety margins defined by the nonclinical toxicology studies that have been conducted to date.

Study Design

A Phase 2, open-label, multiple-dose, dose-escalation study to assess the safety, tolerability, PK, and PD of the compound of Formula (I) in approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH was designed. The study will include a sequential-cohort design with four compound of Formula (I) dose cohorts: 50 mg and 100 mg, with each dose administered for 14 consecutive days:

- Cohort 1: compound of Formula (I) 50 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 2: compound of Formula (I) 100 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 3: compound of Formula (I) 100 mg once daily with the evening meal at approximately 1900 hours.
- Cohort 4: compound of Formula (I) 100 mg twice daily with breakfast at approximately 0700 hours and with the evening meal at approximately 1900 hours.

There will be an approximate 2-week period to evaluate safety and tolerability data before proceeding from Cohort 1 to Cohort 2. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects). Table 27 below depicts the dose cohorts, doses, and number of subjects per cohort.

Table 27. Dose cohorts, doses, and number of subjects

Cohort	Compound of Formula (I) Dose	Approximate Dosing Time(s)	Number of Subjects
1	50 mg	2200 hours	8-10
2	100 mg	2200 hours	8-10
3	100 mg	1900 hours	8-10
4	100 mg	0700 and 1900 hours	Up to 8

Subjects will be screened for eligibility to participate in the study for up to approximately 3 weeks (Days -28 to -8). Subjects who reenroll and have had a stable medication regimen for CAH since their last visit in this study do not have to undergo screening; those who reenroll and have had a change to their medication regimen for CAH must undergo a second screening visit. During screening, subjects will provide a single blood

sample in the morning between 0700 and 1000 hours (prior to first morning dose of hydrocortisone) to determine their 17-hydroxyprogesterone (17-OHP) levels for study entry.

Eligible subjects who have a screening 17-OHP level ≥1,000 ng/dL will be admitted to the study center for 1 night and have baseline serial PD samples collected over a 24-hour period beginning in the evening of Day -7. Baseline serial PD samples will be collected at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

Subjects within each dose cohort will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for CYP21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (the compound of Formula (I) 50 or 100 mg) will be administered at approximately 2200 hours for Cohorts 1 and 2 and at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours for Cohorts 3 and 4. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

Subjects in Cohorts 1 and 2 will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for cytochrome P450 (CYP) 21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (compound of Formula(I) 50 mg or 100 mg) will be administered at approximately 2200 hours. The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 12-hour post-dose PK/PD samples are collected (at approximately 1000 hours) on Day 2 and after the 16-hour post-dose PK/PD samples are collected (at approximately 1400 hours) on Day 15. Subjects will be discharged from the study center the evening on Days 2 and 15 following completion of all study-related procedures for those days. Prior to this discharge on Day 2, study drug will be administered at the study center at approximately 2200 hours. Study drug will then be self-administered nightly at home at approximately 2200 hours on Days 3 to 13. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 3 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center.

Subjects in Cohorts 3 and 4 will have a blood sample collected on Day 1 for CYP21A2 genotyping (only for subjects who have not previously participated in Cohorts 1 or 2). Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. For Cohort 3, study drug (compound of Formula(I) 100 mg) will be administered at home on Days 1 to 13 at approximately 1900 hours with each subject's evening meal. For Cohort 4, study drug compound of Formula(I) 100 mg) will be administered at home on Days 2 to 14 at approximately 0700 hours with each subject's breakfast and on Days 1 to 13 at approximately 1900 hours with each subjects' evening meal. For both cohorts, the Day 14 evening dose will be administered at the study site. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 1 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center. Subjects will be admitted to the study center on Day 14 (last day of dosing). On Day 14, subjects will receive study drug in the study center at approximately 1900 hours with a standard (moderate fat/moderate calorie) evening meal. The subjects' usual morning dose of concurrent steroidal treatments will be administered after PK/PD samples are collected at approximately 1400 hours on Day 15. Subjects will be discharged from the study center the evening on Day 15 following completion of all study-related procedures.

For all cohorts, follow-up visits on Days 21, 28, and 35 will be conducted at the study center or the subject's home by a qualified home healthcare provider (based on the subject's preference). A final study visit will be conducted at the study site approximately 5 weeks after the last dose of study drug (on Day 49 or early termination). There will be a visit window of -8 hours for Day 7, -8 hours/+3 days for Days 21, 28, and 35, and +7 days for the final study visit. Safety, tolerability, PK, and PD will be assessed at scheduled times throughout the study. The study design schematic is shown in FIG. 11.

Dose escalation procedure

Cohort 1 will consist of approximately 8 to 10 subjects who will receive a daily dose of the compound of Formula (I) 50 mg at approximately 2200 hours for 14 days (subjects will receive study drug at the site on Days 1, 2, and 14, and self-administer study drug at home on Days 3 to 13). Following the completion of Day 15 assessments for all subjects in the Cohort 1, a medical monitor will review the accumulated safety and tolerability results to ensure there are no safety concerns with proceeding to the 100 mg dose (Cohorts 2 and 3), and to determine if a maximum tolerated dose (MTD) has been reached. If the MTD is reached, no

dose escalation will occur. There will be an approximate 2-week period between Cohorts 1 and 2 to accommodate this safety review. A similar procedure will be used prior to proceeding to the 100 mg twice daily dose (Cohort 4).

If the medical monitor determines that it is safe to proceed to the compound of Formula (I) 100 mg, subjects in Cohort 2 will be administered the compound of Formula (I) 100 mg daily for 14 days. Dosing for Cohorts 3 and 4 may begin simultaneously with Cohort 2.

During the 14-day dosing period for any cohort, dosing may be postponed or halted if one or more subjects experience a severe or serious adverse event (AE), or if the type, frequency, or severity of AEs becomes unacceptable. If dosing is postponed, the medical monitor will review all available safety, tolerability, and PK data before allowing any further subjects to receive study drug.

Study Population

Approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH, who meet all protocol eligibility criteria, will be enrolled. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects).

Duration of treatment

The expected duration of study participation for each subject is approximately 11 weeks, including up to approximately 3 weeks for screening, a 24-hour PD baseline period (approximately 7 days prior to the first day of dosing), 14 days of dosing, and a follow-up period of approximately 5 weeks. The total duration of the study will be an additional 8 to 11 weeks for subjects who reenroll.

Test product, dose, and mode of administration

The compound of Formula (I) will be supplied as capsules containing 50 mg of the compound of Formula (I) free base for oral administration (see, e.g., Reference 1 formulation as described in Example 9). Doses of the compound of Formula (I) are 50 mg and 100 mg, administered in oral capsule form. Each dose of study drug for Cohorts 1 and 2 is to be administered with a bottle of vanilla-flavored Ensure Plus® (~237 mL). Each dose of study drug for Cohort 3 is to be administered with each subject's evening meal at approximately 1900 hours. Each dose of study drug for Cohort 4 is to be administered with each subject's breakfast at approximately 1900 hours (i.e., a total daily dose of 200 mg).

Criteria for Evaluation

Cohorts 1 and 2

Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 1 to 2 and Days 14 to 15 at: 15 minutes pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours post-dose; Day 7 (at approximately 24 hours post-dose); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours post-dose); and at the final study visit (Day 49 or early termination).

Cohorts 3 and 4

Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 14 to 15 at the following times (for Cohort 4, all times are relative to evening dosing unless otherwise indicated): 15 minutes predose and at 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 23, 24, and 27 hours postdose; Day 7 (at 24 hours postdose for Cohort 3 or at 12 hours post morning dose but prior to the evening dose for Cohort 4); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours postdose); and at the final study visit (Day 49 or early termination).

Pharmacokinetics

The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-tlast}}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours ($AUC_{0\text{–}24}$)
- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)

- Apparent mean residence time (MRT)

Additional PK parameters for Day 14 only:

- Average plasma concentration at steady state (C_{avg})
- Percent fluctuation at steady state (% fluctuation)
- Accumulation index at steady state
- Apparent systemic clearance after oral administration (CL/F) (the compound of Formula (I) only)

Pharmacodynamics

Primary: Morning 17-OHP (serum; ng/dL) from the 0600, 0800, and 1000 hour samples (8-, 10-, and 12-hour post-dose samples from Cohorts 1 and 2 and 11-, 13-, and 15-hour postdose samples from Cohorts 3 and 4.

Secondary: 17-OHP at all other times, androstenedione (serum; ng/dL), testosterone (serum; ng/dL), cortisol (serum; µg/dL), and adrenocorticotropic hormone (plasma ACTH; pg/mL).

Safety

Safety and tolerability will be monitored throughout the study and will include the following assessments:

- Adverse events
- Clinical laboratory tests - clinical chemistry (including creatine kinase, myoglobin, total and conjugated bilirubin), hematology, coagulation (prothrombin time, aPTT, d-dimer, fibrinogen), and urinalysis (including quantitative myoglobin, casts and crystals)
- Vital signs
- Physical examinations (including musculoskeletal exam)
- 12-lead electrocardiograms (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Brief Psychiatric Rating Scale (BPRS)

Statistical methods

Safety, PK, and PD variables will be summarized within each dose cohort (the compound of Formula (I) 50 mg and 100 mg) using descriptive statistics. Summaries of PD measures will include both observed values and changes from pre-dose.

Results

Pharmacokinetic results

Eight subjects (four female and four male) were enrolled in this study and completed Cohort 1. Age, sex, and BMI information for the study participants is shown in Table 28, below.

Table 28. Cohort 1 Subjects

Subject ID	Age (years)	Sex (Male/Female)	BMI (kg/m^2)
001	37	Female	24.9
002	25	Female	32.0
003	49	Male	37.2
004	36	Male	25.0
005	27	Female	25.5
006	19	Male	21.7
007	25	Male	27.5
008	31	Female	34.4

The subjects received a daily dose of the compound of Formula (I) at 50 mg at approximately 2200 hours (~10 p.m. or bedtime) for 14 days. Arithmetic mean values for ACTH (FIG. 12A) and 17-OHP (FIG. 12B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, Day 1, and Day 14. Both ACTH and 17OHP concentration profiles at day 1 and day 14 show clear reductions from the baseline mean profiles. Cohort 1 mean PK parameters of T_{max}, C_{max}, and AUC_{24} for the compound of Formula (I) are shown in Table 29 below. These PK parameters are consistent with observations from Phase 1 studies in healthy volunteers.

Table 29. Cohort 1 Mean PK parameters of T_{max}, C_{max}, and AUC_{24}

	Day 1			Day 14		
	T_{max}	C_{max}	AUC_{24}	T_{max}	C_{max}	AUC_{24}
Mean	**5.4**	**1305**	**10,292**	**4.4**	**1349**	**14,297**
CV%	30	25	24	32	15	24

Additional measurements of cohort 1 and cohort 2 mean PK parameters of T_{max}, C_{max}, and AUC_{24} for the compound of Formula (I) on Day 1 of dosing are shown in Table 30 below.

Table 30: Mean PK parameters of T_{max}, C_{max}, and AUC_{24} on Day 1 of dosing

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure		
Day 1	T_{max}* (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)
G.Mean	6	1,270	10,411	4	2,370	24,725
CV%	-	25	24	-	21	42
N	8	8	8	8	4	4

*Median

Additional measurements of cohort 1, cohort 2 and cohort 3 mean PK parameters of T_{max}, C_{max}, and AUC_{24} for the compound of Formula (I) on Day 14 of dosing are shown in Table 31 below.

Table 31: Mean PK parameters of T_{max}, C_{max}, and AUC_{24} on Day 14 of dosing

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure			Cohort 3 100 mg w/evening Meal		
Day 14	Tmax* (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)	Tmax (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)	Tmax (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)
G. Mean	4	1,335	14,070	4	3,379	35,416	3	3,650	34,706
CV%		15	24		31	37		32	15
N	8	8	8	6	6	6	8	8	8

*Median

Arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, day 1, and day 14. The androstenedione concentration profile on Day 1 and Day 14 shows a clear reduction from the baseline mean profile.

When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of ACTH show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 14A). Arithmetic

mean values across all three timepoints show >=50% reductions from baseline at Day 1 and Day 14 (FIG. 14B).

When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of 17-OHP show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 15A). Arithmetic mean values across all three timepoints show >=40% reductions from baseline at Day 1 and Day 14 (FIG 15B).

When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of androstenedione show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 16A). Arithmetic mean values across all three timepoints show >=30% reductions from baseline at Day 1 and Day 14 (FIG. 16B).

A summary of reduction in 17-OHP and androstenedione in cohort 1 is shown in Table 32. Further, the androstenedione levels of three subjects was normalized by the treatment for the three subjects with Subject ID Nos. 001, 002, and 006).

Table 32. Cohort 1 Summary of Reduction in 17-OHP and Androstenedione at each timepoint in the morning window (6 a.m. to 10 a.m.)

Subject ID	Sex/ Age	Dosing Day	17-OHP % change from baseline			Androstenedione % change from baseline		
			6 AM	8 AM	10 AM	6 AM	8 AM	10 AM
001	F/37	D1 D14	-61.4 -90.3	14.7 -67.2	-24.1 -37.2	-42.0 -84.6	2.0 -58.6	-19.5 -55.1
002	F/25	D1 D14	-96.0 -37.7	-95.5 -58.6	45.4 -24.9	-68.0 -34.2	-66.7 -47.8	-21.7 -38.7
003	M/49	D1 D14	-11.8 -24.5	-46.6 -5.2	-34.0 -22.9	-13.4 -7.5	-47.1 -10.8	-22.7 -16.0
004	M/36	D1 D14	-13.7 -53.6	17.1 -46.8	10.1 -35.8	4.5 -13.8	15.9 -15.2	3.0 -21.2
005	F/27	D1 D14	-24.4 -78.8	-83.6 -95.1	-52.2 -86.3	-35.6 26.7	-50.3 -13.7	-33.5 -10.9
006	M/19	D1 D14	-5.1 -25.4	-1.1 -20.4	-97.8 -98.3	-10.0 -67.8	-18.5 -62.7	-78.9 -92.1
007	M/25	D1 D14	-50.0 14.9	-28.0 4.0	-27.4 -7.1	-24.8 -4.8	-30.0 -36.8	-15.8 -30.2
008	F/31	D1 D14	-64.5 -59.0	-80.7 -65.2	-92.8 -89.1	-12.2 74.5	7.0 99.4	-9.3 59.2

Table 33. Cohort 1 Summary of PK parameters of T_{max}, C_{max}, and AUC_{24} for each subject at days 1 and 14

	Day 1			Day 14		
Subject ID	**T_{max} (h)**	**C_{max} (ng/ml)**	**AUC_{24} (h*ng/ml)**	**T_{max} (h)**	**C_{max} (ng/ml)**	**AUC_{24} (h*ng/ml)**
001	6	1830	14,487	6	1570	20,863
002	6	1210	11,829	4	1610	15,494
003	6	1060	11,068	3	1310	15,599
004	4	1670	9,669	3	1160	10,180
005	8	961	9,266	6	1550	15,130
006	4	1030	6,574	3	1090	10,288
007	6	1550	8,239	6	1170	12,880
008	3	1130	11,209	4	1330	13,944
Mean	**5.4**	**1305**	**10,292**	**4.4**	**1349**	**14,297**
CV%	30	25	24	32	15	24
N	8	8	8	8	8	8

After 14 days of once-daily compound of Formula (I) administration, a majority of participants in Cohorts 1-3 showed reduced serum concentrations of adrenal androgens and precursors. Mean changes from baseline (±standard deviation) in Cohort 1 were as follows: 17-OHP, -2341.0±1535.0 ng/dL; androstenedione, -98.4±98.7 ng/dL; and ACTH, -157.0±194.9 pg/mL. Mean reductions were larger in Cohort 2 (17-OHP, -4406.0±5516.1; androstenedione, -362.8±354.0; ACTH, -180.9±155.2) and Cohort 3 (17-OHP, -4760.1±4018.2; androstenedione, -210.9±188.6; ACTH, -358.9±177.6), suggesting a possible dose response. FIGs. 17A-17C, 18A-18C, and 19A-19C depict results from Cohorts 1, 2, and 3, respectively.

Summary

The results from this ongoing Phase II open-label study demonstrated a reduction of at least 50 percent from baseline in 17-hydroxyprogesterone (17-OHP) and adrenocorticotropic hormone (ACTH) levels in more than 50 percent of CAH patients in cohort 1 treated with the compound of Formula (I) for 14 days (i.e., 6 of 8 patients in cohort 1 had a reduction of ≥50% from baseline levels of 17-OHP during at least one morning window timepoint, see, e.g., Table 32). Meaningful reductions were also observed in other biomarkers, including androstenedione (i.e., 4 of these patients also had a reduction of ≥50% from baseline levels of androstenedione during at least one morning window timepoint, see, e.g., Table 32). The greater reductions in biomarkers in cohorts 2 and 3, treated with double the dose of the compound of Formula (I)

compared with cohort 1, suggest a possible dose response. Further, the compound of Formula (I) was well-tolerated with a relatively small number of mild adverse events (AEs) reported (e.g., headache, ovulation pain, fatigue, localized infection (toe), dizziness, nausea, URI, contusion with the most common being headache). No clinically significant findings from routine labs, vital signs, or electrocardiograms were found.

Example 9: Reference Formulation 1 of the compound of Formula (I)

Tables 34A and 34B show Reference formulation 1 of the compound of Formula (I) as used in the clinical studies described in Examples 6 and 8, above. An example manufacturing process is shown in FIG. 20. Another example manufacturing process is shown in FIG. 21.

Table 34A:

Component	**Quality Standard**	**Function**	**50 mg Capsule**	
			Weight (mg/unit)	**% (w/w)**
Compound of Formula (I), free base	In-house	Active Ingredient	50.0	10.0
Medium-Chain Triglycerides (Labrafac TM Lipophile WL1349)	NF	Oily Phase Vehicle	196.0	39.2
Propylene Glycol Dicaprylate/Dicaprate, (LabrafacTM PG)	NF	Emulsifying Agent	102.0	20.4
Lauroyl Polyoxyl-32 Glycerides (Gelucire® 44/14)	NF	Nonionic Surfactant & Solubilizing Agent	95.0	19.0
Vitamin E Polyethylene Glycol Succinate (Kolliphor® TPGS)	USP/NF	Solubilizing Agent	57.0	11.4
Total Emulsion Weight			**500.0**	**100.0**
Gelatin Capsule Shell. Size #00, Swedish Orange cap/body; (Coni-Snap®)	Non Pharmacopoeial	Capsule Shell	--	--

Gelatin Powder, 220 Bloom	USP	Capsule shell banding agent	--	--
Purified Water	USP	Capsule shell banding solvent	--	--

Table 34B:

Component	**Quality Standard**	**Function**	**50 mg Capsule**	
			Weight (mg/unit)	**% (w/w)**
Compound of Formula (I), free base	In-house	Active Ingredient	50.0	10.0
Medium-Chain Triglycerides (caprylic:capric acid 60:40; Miglyol 812N)	Ph. Eur./NF	Vehicle	195.85	39.2
Propylene Glycol Dicaprylocaprate, (LabrafacTM PG)	Ph. Eur.	Vehicle	102.15	20.4
Lauroyl macrogolglycerides type 1500-Lauroyl polyoxylglycerides type 1500 (Gelucire® 44/14)	Ph. Eur./NF	Surfactant	95.0	19.0
Vitamin E Polyethylene Glycol Succinate, 260 mg/g *d*-alpha tocopherol (Vitamin E/TPGS 260)	NF	Surfactant	57.0	11.4
Total Emulsion Weight			**500.0**	**100.0**
Orange opaque hard capsule, size 0, composed of gelatin, titanium dioxide and red ferric oxide (Swedish Orange ®)	Non Pharmacopoeial	Capsule Shell	--	--
Ethanol (96%) and Purified Water	USP	Capsule shell banding solvent	--	--

Example 10: Study Evaluating Effect of Ensure Plus, Ensure Pudding, Milk and High Fat Meal on Reference Capsule

Study design

This is a Phase 1, open-label, randomized, four-period crossover study to evaluate the effect of food with different levels of fat and caloric content on the PK, safety, and tolerability of the compound of Formula (I) in healthy adult subjects.

A total of 16 healthy adult subjects (8 males and 8 females) will be randomly assigned to 1 of 4 treatment sequences (4 subjects per sequence [2 males and 2 females per sequence]; see Table 35 below). During each treatment period, subjects will receive a single dose of the compound of Formula (I) 100 mg administered with the appropriate meal, according to the randomization scheme. There will be a washout of at least 21 days between each dose.

Table 35:

Treatment Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
1	Reference meal	Test meal 1	Test meal 2	Test meal 3
2	Test meal 1	Test meal 3	Reference meal	Test meal 2
3	Test meal 2	Reference meal	Test meal 3	Test meal 1
4	Test meal 3	Test meal 2	Test meal 1	Reference meal

Reference meal: vanilla-flavored Ensure Plus® Test meal 1: Low fat, low caloric content meal 1 Test meal 2: Low fat, low caloric content meal 2
Test meal 3: standard high fat, high caloric content meal

After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days before Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1 and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During each treatment period, subjects will fast overnight for at least 10 hours until the start of the assigned meal, according to the randomization scheme, and ingest the study drug at approximately 0800 hours. Subjects must complete the entire meal within the specified time period and should not consume any other food for 4 hours after dosing. For all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water provided with study drug dosing and planned meals.

On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 100 mg. Blood samples will be collected for PK analysis over a period of 36 hours during the in-house stay. During each treatment period, subjects will remain in the clinic on the day of dosing and will be discharged on Day 2 after completing all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects will return for an outpatient visit to the clinic for PK blood sample collection and safety assessments. On Day 21 of treatment periods 1 to 3, subjects will arrive at the site and have Day 21 assessments completed and they will stay overnight at the site and begin Day 1 of the subsequent treatment period the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 4 (21 ± 2 days after treatment period 4 dosing) or upon early termination.

Blood samples for PK d/conducted at scheduled times throughout the study.

Study population

Sixteen healthy adult subjects (8 males and 8 females) between 18 and 55 years of age, inclusive, who meet all protocol eligibility criteria, will be enrolled.

Duration of treatment

The expected duration of study participation for each healthy adult subject will be approximately 16 weeks, including up to 28 days of screening, 4 days of dosing with at least 21 days between consecutive doses, and a final follow-up study visit 21 days (± 2 days) after receiving the last dose of study drug during treatment period 4.

Test product, dose, and mode of administration

The compound of Formula (I) will be supplied as capsules for oral administration (encapsulated, lipidic semi-solid formulation, e.g., Example 9). The compound of Formula (I) capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. During each treatment period, subjects will receive two 50 mg capsules (100 mg) of the study drug along with a meal and water as defined by the randomization scheme. The food, water, and study drug administration are as follows:

Reference meal: Two capsules of study drug will be administered approximately 5 minutes after the start of a liquid dietary supplement (i.e., Ensure Plus® [237 mL container]) and an additional 120 mL of water for study drug dosing.

Test meal 1: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 1 with 120 mL of water for study drug dosing.

Test meal 2: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 2 with 120 mL of water for study drug dosing.

Test meal 3: Two capsules of study drug will be administered approximately 30 minutes after the start of a high fat, high caloric meal with 120 mL of water for study drug dosing.

CRITERIA FOR EVALUATION

Pharmacokinetics

Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-}tlast}$)
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)
- Molar AUC ratio of primary metabolite(s) to the parent drug compound of Formula (I). The following plasma PK parameters will be calculated only for the compound of Formula (I):
- Apparent systemic clearance after oral administration (CL/F)

- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

Safety Assessments

Safety will be monitored throughout the study and will include the following assessments:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiograms (ECGs)

Statistical methods

Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by meal type (test meal/reference meal) using descriptive statistics. Two-sided 90% confidence intervals will be calculated for the ratio of each test meal versus the reference meal for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} for the compound of Formula (I) and metabolites. Safety data will be summarized with descriptive statistics.

Results

Pharmacokinetic results

Pharmacokinetic results are shown in Table 36 below.

Table 36: Summary of Plasma Pharmacokinetic Parameters

		Compound of Formula (I) Plasma Concentration		
Parameter (units) Statistic	**Ensure Plus (Fed) (N=18)**	**Ensure Pudding (Fed) (N=18)**	**Whole Milk (Fed) (N=17)**	**High Fat Meal (Fed) (N=17)**
$AUC_{0-tlast}$ (ng×hr/mL)				
Mean (SD)	36703 (17400)	34077 (11597)	35561 (15866)	55487 (23242)
Geom CV(%)	58	39.7	44.6	41.9

$AUC_{0-\infty}$ (ng×hr/mL)				
Mean	45386 (19648)	40037 (9515)	46737 (17395)	63755 (19139)
Geom CV(%)	43.3	23.8	38.8	31
C_{max} (ng/mL)				
Mean (SD)	3090 (1070)	3038 (984)	2835 (1005)	4336 (1938)
Geom CV(%)	39.7	34.9	34.5	53.6
t_{max} (hr)				
Median (min,max)	5.0 (2.0, 10.0)	5.0 (4.0, 6.0)	5.0 (4.0, 7.0)	5.0 (4.0, 7.0)
T_{lag} (hr)				
Mean (SD)	0.38 (0.46)	0.20 (0.25)	0.16 (0.31)	0.29 (0.37)
$t_{½}$ (hr)				
Mean (SD)	361 (263)	373 (196)	373 (143)	326 (120)
Geom CV(%)	61.1	48.6	37.1	33.8
CL/F (L/hr)				
Mean (SD)	2.49 (0.956)	2.636 (0.659)	2.427 (0.975)	1.706 (0.526)
Geom CV(%)	41.2	24.8	38.8	31.1
Vz/F (L)				
Mean (SD)	1254 (906)	1414 (720)	1308 (627)	816 (378)
Geom CV(%)	72.7	58.4	61.3	54.9

Example 11: Spray-dried Dispersion Granule Formulation of the Compound of Formula (I) (SDD-G)

Table 37 shows a granule formulation of the compound of Formula (I) using a SDD prepared according to Example 3, above. An example manufacturing process is shown in FIG. 22A and FIG. 22B.

Table 37:

Component	Quality Standard	Function	50 mg Sachet		Batch Weight (g)
			Weight (mg/unit)	% (w/w)	
Example 3, SDD	In-house	Drug Substance	200.0	13.33	40
Calcium Silicate (ZEOPHARM 250)	NF	Glidant	10.0	0.67	2
Mannitol (Pearlitol 200SD)	NF / EP / JP	Filler	832.5	55.5	166.5
Microcrystalline Cellulose (Avicel PH-102)	NF / EP / JP	Filler	300.0	20.0	60
Croscarmellose Sodium (Ac-Di-Sol®) SD711	NF / EP / JP	Disintegrant	150.0	10.0	30
Sodium Stearyl Fumarate	NF / EP / JP	Lubricant	7.5	0.5	1.5
Total			1500	100.0	300

Example 12: Liquid Formulation 1 of the Compound of Formula (I)

Table 38 shows liquid formulation 1 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 23.

Table 38:

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Compound of Formula (I) FB	In-house	Drug Substance	50.0	5	20.03
Saccharin	NF / EP	Sweetener	1.5	0.15	0.61
Butylated hydroxytoluene	NF / EP	Anti-oxidant	1.7	0.17	0.69
FONA orange flavor	NF	Flavor	1.0	0.1	0.41
Labrafac Lipophile WL1349	NF / EP	Liquid Vehicle	to 1 mL	94.58	358.87
Total			1 mL	100.0	380.6

Example 13: Liquid Formulation 2 of the Compound of Formula (I)

Table 39 shows liquid formulation 2 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 24.

Table 39:

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Compound of Formula (I) FB	In-house	Drug Substance	50.0	5	20.17
Saccharin	NF / EP	Sweetener	1.5	0.15	0.61
Butylated hydroxytoluene	NF / EP	Anti-oxidant	1.7	0.17	0.68
LABRAFIL M 1944 CS	NF / EP	Surfactant	200.0	20	80.16
FONA orange flavor	NF	Flavor	1.0	0.1	0.40
Labrafac Lipophile WL1349	NF / EP	Liquid Vehicle	to 1 mL	74.58	278.68
Total			1 mL	100.0	380.7

Example 14: A Phase I, Open-Label Study to Evaluate the Pharmacokinetics, Relative Bioavailability, Effect of Food, Safety and Tolerability of Different Compound of Formula (I) Prototype Formulations in Healthy Adult Subjects.

Methodology

This is a single center, open-label, randomized, single dose 4-period crossover study in healthy adult subjects designed to investigate the pharmacokinetic (PK) and safety of up to 4 compound of Formula (I) liquid lipidic prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulations, 50 mg/mL), a compound of Formula (I) spray dried dispersion formulation (compound of Formula (I) Granule for Sprinkle, 25 – 50 mg) and compound of Formula (I), 50 mg Capsules (Reference). It is planned to enroll 36 subjects to be allocated as 3 cohorts of 12 subjects per cohort, with 6 sub-cohorts of 6 subjects per sub-cohort. In each of these 6 sub- cohorts, 6 subjects will be assigned to one of 3 sub-cohorts where a single oral dose of Investigational Medicinal Product (IMP) is administered in 4 dosing periods (Periods 1 to 4) in multiple fed or fasted states or to one of 3 sub-cohorts where a single oral dose of IMP is administered in 2 dosing periods (Periods 1 and 2) only in

the fed state. Within each sub-cohort, subjects will also be randomized before administration of the first dose of IMP in Period 1 to one of the following treatment sequences (Table 40):

Table 40:

Sub-Cohort	Sequence	Number of Subjects	Total Number of Periods Dosed	Regimen			
				Period 1	Period 2	Period 3	Period 4
1A	ABEF	3	4	Regimen A	Regimen B	Regimen E	Regimen F
	BAEF	3	4	Regimen B	Regimen A	Regimen E	Regimen F
1B	AB	3	2	Regimen A	Regimen B	N/A	N/A
	BA	3	2	Regimen B	Regimen A	N/A	N/A
2A	ADEF	3	4	Regimen A	Regimen D	Regimen E	Regimen F
	DAEF	3	4	Regimen D	Regimen A	Regimen E	Regimen F
2B	AD	3	2	Regimen A	Regimen D	N/A	N/A
	DA	3	2	Regimen D	Regimen A	N/A	N/A
3A	ACEF	3	4	Regimen A	Regimen C	Regimen E	Regimen F
	CAEF	3	4	Regimen C	Regimen A	Regimen E	Regimen F
3B	AC	3	2	Regimen A	Regimen C	N/A	N/A
	CA	3	2	Regimen C	Regimen A	N/A	N/A

At informed consent, subjects will agree either to participate in 2 study periods or 4 study periods. Once placed into a sub-cohort, the order in which subjects receive the study treatments will be randomized based on the schedule above.

Subjects will receive up to 4 regimens in up to 4 periods in an order according to the randomization schedule within each sub-cohort.

The effect of different prandial states on the PK of the compound of Formula (I) may be explored in Periods 3 and 4 by administering in the fasted state or after an alternative meal (e.g. high fat, standard or light breakfast, etc.).

The proposed regimens are presented in Table 41 below:

Table 41:

Regimen	Investigational Medicinal Product	Dose	Route of Administration	Prandial State
A	Compound of Formula (I), 50 mg Capsules (Reference)	50 mg	Oral	Fed (Ensure Plus)
B	Compound of Formula (I) Oral Solution, Prototype Formulation 1, 50 mg/mL	50 mg	Oral	Fed (Ensure Plus)
C	Compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL	50 mg	Oral	Fed (Ensure Plus)
D	Compound of Formula (I) Granule for Sprinkle, 25 – 50 mg	50 mg	Oral	Fed (Ensure Plus)
E	Compound of Formula (I) Oral Solution, Prototype Formulation 1	100 mg	Oral	Fed (Ensure Plus)
F	Compound of Formula (I) Oral Solution, Granule for Sprinkle	50 mg	Oral	Fed (alternative meal)

Study Design:

Subjects will be screened for eligibility to participate in the study up to 28 days before the first dose of IMP in Period 1. Each study period will follow the same study design. Subjects will be admitted to the clinical unit on the evening prior to IMP administration (Day -1). For Periods 1 and 2 (Regimen A and one of either Regimens B, C or D), all subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement (Ensure Plus). For Periods 3 and 4 (Regimens E and F), subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement or an alternate prandial state (fasted or alternative meal). IMP administration will be performed on Day 1 with an appropriate interval between subjects based on logistical requirements (approximately 10 min). Meals will be standardized for each treatment regimen across periods.

Subjects will remain in the clinical unit until 36 h post-dose when they will be discharged. Subjects will return to the clinical unit at 168 h (7 days) and 336 h (14 days) post-dose for a PK blood sample and safety assessments. The minimum washout between IMP

dosing occasions will be 14 days between Periods 1 and 2 and 21 days or more to accommodate interim data reviews between Periods 2 and 3 and between Periods 3 and 4.

There will be a follow-up phone call 18 to 24 days post-final visit to ensure the ongoing wellbeing of subjects.

Following the completion of Period 2 for all cohorts, there will be an interim data review during which the PK and safety data will be reviewed, plus any relevant emerging Chemistry, Manufacturing and Control (CMC) stability study information, to determine the formulation, dose level and prandial state in which to administer the IMP in Period 3 (Regimen E). There will be a similar interim review following completion of Period 3 (administration of Regimen E) to determine the formulation, dose level and prandial state in which to administer the IMP in Period 4 (Regimen F). The criteria for the interim decisions will be based on available compound of Formula (I) PK data: e.g., C_{max}, T_{max}, AUC(0-36), F_{rel} and safety data.

Number of Subjects Planned:

It is planned to enroll 36 healthy male and female (non-pregnant, non-lactating) subjects in 6 sub-cohorts of 6 subjects per sub-cohort. These sub-cohorts will be combined in sets of 2 to create 3 cohorts of n = 12 for Periods 1 and 2 to target data in 10 evaluable subjects in each cohort for the primary objectives per formulation variant. A total of 18 subjects, 6 from each of Sub-Cohorts 1A, 2A and 3A participating in Periods 1 and 2, will additionally participate in Periods 3 and 4 with a target of a minimum of 6 evaluable subjects. A subject will be considered evaluable for a particular regimen if they have received an IMP and has completed sufficient planned PK assessments up to 336 h (14 days) after dosing for that regimen to allow for the assessment of study endpoints. A subject will be considered evaluable for a particular comparison (e.g., food effect, relative bioavailability) if they have received both IMPs under comparison and have sufficient PK data up to 14 days after each regimen to allow for assessment of study endpoints.

Subjects withdrawn due to an IMP-related adverse event (AE) will not be replaced. Subjects who are withdrawn for other reasons may be replaced as required by agreement between the principal investigator (PI) and sponsor to ensure sufficient numbers of evaluable subjects at the end of each study period. Replacement subjects may be required to be dosed with specific formulations from the previous regimens in order to obtain the minimum number of evaluable subjects required for interim decisions and to obtain data in any other regimen that is required to fulfil the study objective comparisons, with the exception that any

previously dosed IMP that has been considered sub-optimal will not be dosed. Up to 8 replacement subjects in total may be enrolled into the study. The maximum number of subjects that may be dosed is 44 in total.

If a subject withdraws from Sub-Cohort 1A, 2A or 3A after Period 2, it is acceptable to replace them with a subject from Sub-Cohort 1B, 2B or 3B provided the subject signs an updated consent form agreeing to participate in four treatment periods. At the discretion of the investigator, such a subject may not be required to undergo repeat screening procedures.

Duration of Study:

For subjects enrolled to receive single dose administration on 4 separate occasions in Periods 1 to 4 (Sub-Cohorts 1A, 2A and 3A), the estimated time from screening until the follow-up phone call is approximately 15 to 16 weeks.

For subjects enrolled to receive single dose administration on 2 separate occasions in Periods 1 to 2 only (Sub-Cohorts 1B, 2B and 3B), the estimated time from screening until the follow-up phone call is approximately 8 to 9 weeks.

Pharmacokinetic Assessments:

The plasma concentration data for a compound of Formula (I) will be analyzed for final reporting by Quotient Sciences and for interim reviews by Neurocrine Biosciences, Inc. (NBI), using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA). NBI will be responsible for PK analysis for interim review.

PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the following PK parameters (Table 42) where possible and appropriate:

Table 42:

T_{lag}	Time prior to the first measurable (non-zero) concentration
T_{max}	Time to maximum plasma concentration
C_{max}	Maximum plasma concentration
$AUC_{0\text{-}tlast}$	Area under the plasma concentration versus time curve (AUC) from 0 h to last measurable concentration

$AUC_{0\text{-}inf}$	AUC from 0 h extrapolated to infinity
AUC_{extrap}	Percentage of AUC_{0-inf} extrapolated beyond the last measurable concentration
Lambda-z	Slope of the apparent terminal phase
$T_{1/2}$	Apparent terminal half-life
CL/F^a	Apparent systemic clearance after oral administration
Vd/F^a	Apparent volume of distribution based on the area after a single oral administration
MRT	Mean residence time
MPR $AUC_{0\text{-}tlast}$	Metabolite to parent ratio based on $AUC_{0\text{-}tlast}$
MPR $AUC_{0\text{-}inf}$	Metabolite to parent ratio based on $AUC_{0\text{-}inf}$

Taste Assessments:

Taste will be assessed for each IMP formulation and vehicle (e.g., Ensure Plus, soft food) using a questionnaire designed for this purpose and adapted for this specific study as required.

The questionnaire will ask subjects to rate the acceptability of smell, sweetness, bitterness, flavor, mouth feel, and aftertaste on a 6-point scale, and overall experience on a 5-point scale for each IMP formulation independently of any previous formulations.

Statistical Methodology:

Descriptive summaries for all safety data, PK assessments and taste questionnaire data will be provided. No hypothesis testing will be performed for the safety or taste questionnaire data.

Periods 1 and 2 – for Each Cohort Separately

Relative Bioavailability

Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability (Frel) using a mixed effects model with terms for regimen, period and

sequence as fixed effects and subject within sequence as a random effect. Ratios of geometric means (GMRs) and 90% confidence interval (CI) for the relevant comparison of interest, i.e., between each of the prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulation 1, 50 mg/mL, e.g., Example 12; compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL, e.g., Example 13; and compound of Formula (I) Granule for Sprinkle, 25 – 50 mg, e.g. Example 11 [Regimens B, C and D, respectively]) and compound of Formula (I), 50 mg Capsules, e.g., Example 9 (Reference; Regimen A) will be presented.

All Periods (Periods 1 to 4)

Food Effect

Statistical modelling will be performed on the compound of Formula (I) PK parameters AUC(0-tlast), AUC(0-inf) and Cmax to assess for the effects of food, if relevant. The natural log-transformed PK parameters will be analyzed for bioavailability using a mixed effects model with terms for prandial state (and meal type if applicable) as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparisons of interest will be presented where the ratio is defined as fasted/fed or test meal/reference meal (if applicable).

Relative Bioavailability

Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability using a mixed effects model with terms for regimen as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparison of interest i.e., between each of the prototype formulations (Regimens E and F, IMPs to be determined by interim reviews following completion of Periods 2 and 3) and compound of Formula (I), 50 mg Capsules (Reference; Regimen A) will be presented.

Results

Preliminary PK data is summarized in Table 43 below:

Table 43: Preliminary Data from Periods 1 and 2

	A- Reference	B-Oral Solution 1	C-Oral Solution 2	D- SDD Granule
N	35	12	12	12
Tmax * (h)	5 (2,6)	6 (5,7)	5 (5,7)	5 (5,7)
Cmax (ng/ml)	1361 (33)	790 (31)	1082 (46)	1075 (35)
AUC36 (h*ng/ml)	9452 (30)	5556 (34)	7582 (37)	6691 (41)

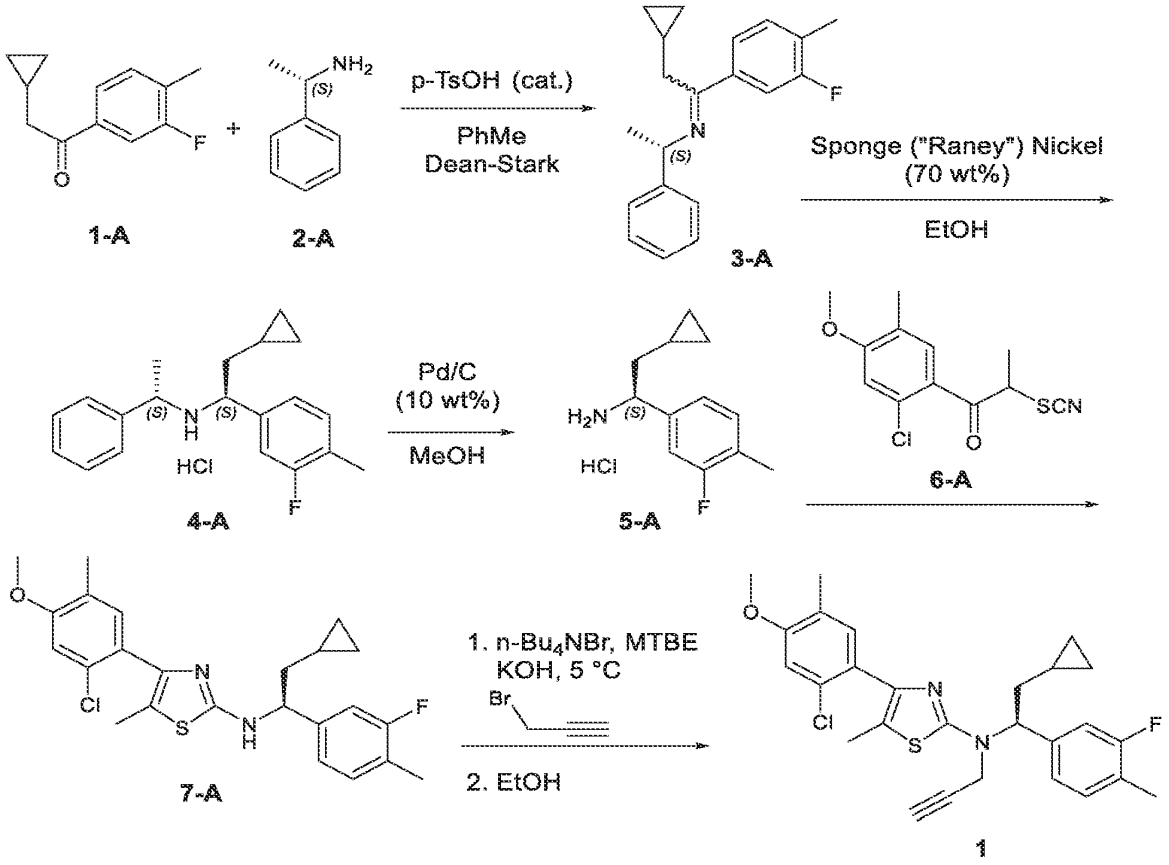
*Geometric Mean /CV% for AUC and Cmax; Median for Tmax

Example 15. Compound of Formula (I) Crystalline Free Base Form I

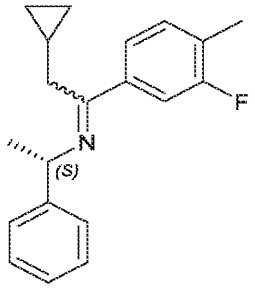
Example 15A

Scheme 1: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), Form I)

Scheme 1



Step 1: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-(1-phenylethyl)ethan-1-imine (Compound 3-A)

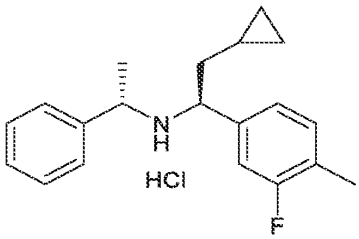


Compound 3-A

A mixture of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (1-A, 150.7 kg, 1 eq., as a 27.6% w/w solution in toluene, Example 15C), (*S*)-(−)-1-Phenylethylamine (2-A, 112.9 kg, 1.19 eq.), and *p*-toluenesulfonic acid (7.4 kg, 0.05 eq.) is refluxed at 110 – 120 °C for 23 – 25 h in a reactor set up in a Dean-Stark configuration. The solvent is then removed

at 125 – 135 °C under atmospheric pressure until distillation halts and a portion of toluene (275 kg, 2.24 w/w) is added to afford a suspension. The suspension is refluxed at 110 – 120 °C for 23 – 25 h. The mixture is cooled to 22 °C and washed twice with aqueous NH_4Cl (10%, 301.2 kg, 0.72 eq.) and once with aqueous $NaHCO_3$ (5%, 301.2 kg, 0.23 eq., check pH 8 – 9). The solvent is removed at 125 – 135 °C and atmospheric pressure to a target volume of 256 L, the mixture is filtered over celite, the cake is washed with toluene (25 kg). The resulting mixture containing compound 3-A is used directly in the next step without isolation. The yield is determined by correcting for the LOD and GC-FID purity of the sample (208.4 kg, 90.0% corrected, 0.89% Compound 2-A). EI-MS: 294.1 $[M-H]^+$, 190.1 $[M-C_6H_5CH(CH_3)]^+$, 105.1 $[C_6H_5CH(CH_3)]^+$.

Step 2: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-((*S*)-1-phenylethyl)ethan-1-amine hydrochloride (Compound 4-A)

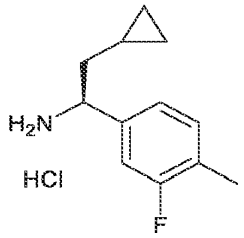


Compound 4-A

Sponge nickel catalyst (144 kg, 0.70 w/w, shipped as a 50% w/w suspension in water) is added to a hydrogenation reactor, equipped with a dip tube capable of removing material from the top of the mass inside, minimizing the amount of water introduced. The supernatant is discarded, ethanol (329.3 kg, 1.58 w/w, anhydrous) is added, the suspension is stirred and then allowed to settle. This process is repeated four more times and the Karl Fisher (KF) of the supernatant is checked (≤ 1% H_2O w/w). Compound 3-A (208.4 kg, 1 eq., as a 62.6% solution in toluene) is added to the mixture in the hydrogenation reactor and ethanol (387.6 kg, 1.86 w/w) is used to rinse the addition flask into the hydrogenation reactor. The hydrogenation reactor is pressurized/depressurized twice with nitrogen (2 bar) and twice with hydrogen (5 bar) then pressurized with hydrogen (9.8 – 10.2 bar) and heated to 33 – 37 °C and stirred for 17 – 19 h. The system is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed with three times with ethanol (493.8 kg, 2.37 w/w). HCl (concentrated, 83.4 kg, 1.07 eq.) is added and the mixture stirred 25 – 35 min at 20

– 24 °C. The mixture is concentrated by distillation at 78 – 80 °C and atmospheric pressure to remove water with a distillate target volume of 1167 L (5.6 L/kg, Compound 3-A) and the KF of the solution is checked (≤ 1.5% H_2O w/w). The mixture is stirred at 48 – 52 °C for 55 - 65 min, then 68 – 72 °C for 55 – 65 min, then cooled to 20 – 24 °C at a rate of 12 °C/h and stirred for 25 – 35 min, then cooled to 0 – 4 °C at a rate of 10 °C/h and stirred for 55 – 65 min. The suspension is filtered, the cake is washed twice with precooled ethanol (329.2 kg, 1.58 w/w, 0 °C), and the collected solid is dried at 40 °C to afford compound 4-A (156.5 kg, 66.4% uncorrected). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm -0.33 - -0.06 (m, 2 H) 0.11 - 0.31 (m, 3 H) 1.57 (d, *J*=6.57 Hz, 3 H) 1.95 (br t, *J*=7.07 Hz, 2 H) 2.26 (d, *J*=1.26 Hz, 3 H) 3.68 (br d, *J*=7.83 Hz, 1 H) 3.92 (br t, *J*=6.44 Hz, 1 H) 6.98 (dd, *J*=7.71, 1.14 Hz, 1 H) 7.28 - 7.36 (m, 2 H) 7.37 - 7.50 (m, 5 H). ESI-MS: 298.2 m/z $[M+H]^+$.

Step 3: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-amine hydrochloride (Compound 5-A)

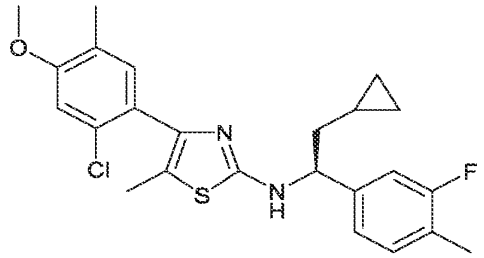


Compound 5-A

Compound 4-A (156.5 kg, 1.00 eq.) and Pd/C (7.8 kg, 10% Pd basis) are added to an inerted hydrogenation reactor. The reactor is then pressurized/depressurized twice with nitrogen (2 bar) and then methanol (494.5 kg, 3.16 w/w) is added. The reactor is depressurized/pressurized three times with nitrogen (2 bar) then three times with hydrogen (5 bar), pressurized with hydrogen (9.8 – 10.2 bar), heated to 58 – 62 °C and stirred for 7 – 9 h. The reaction mixture is cooled to 20 – 24 °C. The reactor is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed three times with methanol (492.9 kg, 3.15 w/w). The solution is concentrated at 63 – 67 °C and atmospheric pressure to a distillate target volume of 1408 L (9.0 L/kg Compound 4-A). *n*-Heptane (1173.8 kg, 7.5 w/w) is added and the mixture is refluxed at 65 – 80 °C and atmospheric pressure in Dean-Stark configuration to remove methanol. The suspension is cooled to 31 – 35 °C and filtered, the cake washed with *n*-heptane (147.1 kg, 0.94 w/w), and the solid dried at 40 °C

(101.0 kg, 93.8% uncorrected, 99.2% *ee*). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm -0.12 - 0.14 (m, 2 H) 0.26 - 0.42 (m, 2 H) 0.44 - 0.55 (m, 1 H) 1.70 - 1.83 (m, 2 H) 2.23 (d, *J*=1.52 Hz, 3 H) 4.24 (t, *J*=7.33 Hz, 1 H) 7.22 - 7.29 (m, 1 H) 7.29 - 7.36 (m, 1 H) 7.40 (dd, *J*=10.99, 1.39 Hz, 1 H). ESI-MS: 194.2 $[M+H]^+$, 177.0 $[M-NH_2]^+$.

Step 4: Preparation of (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (Compound 7-A)

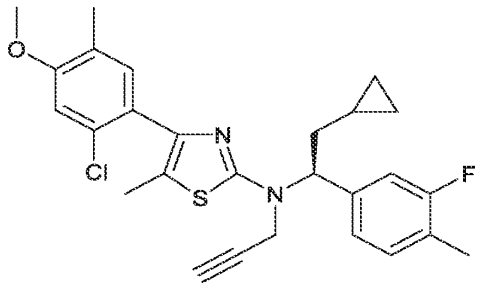


Compound 7-A

A mixture of *n*-heptane (146 kg), water (142 kg), Compound 5-A (57.4 kg), and aqueous sodium hydroxide (30% w/w, 41.0 kg) was stirred together. The layers were partitioned, and the aqueous layer removed. The organic layer was washed with water (170 kg) and the layers partitioned. The organic layer was set aside using n-heptane (40 kg) to rinse and n-heptane (145 kg) and 1-(2-chloro-4-methoxy-5-methylphenyl)-2-thiocyanatopropan-1-one (6-A, 66.1 kg) were added to the reactor and heated to 85 °C. The previously set aside organic layer containing the free base of Compound 5-A was added at 84 – 85 °C to the reactor and rinsed with n-heptane (20 kg). The resulting mixture was stirred for 2 h at 83 °C. Subsequently, the solvent was switched to methanol by four put-and-take additions/vacuum distillations of methanol (180 kg) at 55 °C with the target volume being 287 L remaining in the reactor. The suspension was cooled to 5 °C and water (570 kg) was added over 4 h at 5 – 10 °C, with the first 60 kg added very slowly. The suspension was aged 2 h at °C and then isolated by filtration and washed with a mixture of methanol/water (91/115 kg) and then a mixture of methanol/water (134/57 kg). The yellow solid was dried at 25 °C and 1 mbar for 17 h then 40 °C and 1 mbar for 22 h to afford Compound 7-A (97.4 kg, 87.5% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm -0.01 - 0.14 (m, 2 H) 0.29 - 0.42 (m, 2 H) 0.61 - 0.73 (m, 1 H) 1.47 (dt, *J*=13.83, 6.85 Hz, 1 H) 1.76 (dt, *J*=13.89, 7.20 Hz, 1 H) 2.00 (s, 3 H) 2.11 (s, 3 H) 2.19 (d, *J*=1.01 Hz, 3 H) 3.82 (s, 3 H) 4.54 (q, *J*=7.58 Hz, 1 H) 7.00 (s,

1 H) 7.06 (d, *J*=0.76 Hz, 1H) 7.08 - 7.14 (m, 2 H) 7.18 - 7.23 (m, 1 H) 7.89 (d, *J*=8.08 Hz, 1 H). ESI-MS: 445.3 m/z $[M+H]^+$.

Step 5: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I))



Compound of Formula (I)

A mixture of MTBE (279 kg), tetra-n-butylammonium bromide (10.5 kg), and Compound 7-A (95.4 kg) were heated at 60 °C external temperature for 30 min and then cooled to 0 °C. Aqueous potassium hydroxide (52.4% w/w, 364 kg) and propargyl bromide (39.4 kg as an 80% w/w solution in toluene, 1.19 eq.) were added at 0 – 5 °C and the biphasic mixture aged 14.5 h at 4 – 6 °C with vigorous stirring. Subsequently, water (191 kg) was added and the aqueous layer was discharged. The organic layer was washed twice with water (382 kg) and once with aqueous acetic acid (5.26% w/w, 190 kg) at 20 °C. The mixture is polish filtered, rinsed with ethanol (11 kg) and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol (300 kg) at 25 – 30 °C for the first cycle and then 35 – 40 °C with the target volume of each cycle being 250 L remaining in the reactor. Ethanol (164 kg) was added and the mixture heated at 60 °C external for 0.5 h before it was cooled to 25 °C in 1 h and seeded with authentic compound of Formula (I) (0.340 kg) which may be prepared as described below in Example 15B. The suspension was aged for 5 h, cooled to 0 °C in 2 h, aged 12 h, filtered, and washed twice with ethanol (24 kg each) pre-cooled to 0 °C. The white solid was dried at 40 °C and 1 mbar for 19 h to yield 80.15 kg of the compound of Formula (I), Form I (77.2% yield). ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.14 (qt, *J*=8.59, 4.42 Hz, 2 H) 0.29 - 0.48 (m, 2 H) 0.61 - 0.82 (m, 1 H) 1.89 (dt, *J*=14.08, 6.98 Hz, 1 H), 2.07 (br d, *J*=7.83 Hz, 1 H) 2.10 (s, 3 H) 2.14 (s, 3 H) 2.20 (d, *J*=1.01 Hz, 3 H)

3.11 (t, *J*=2.27 Hz, 1 H) 3.83 (s, 3 H) 3.94 - 4.22 (m, 2 H) 5.26 (t, *J*=7.58 Hz, 1 H) 7.05 (s, 1 H) 7.10 - 7.36 (m, 4 H). ESI-MS: 483.2 m/z $[M+H]^+$.

The crystallinity of the crystalline free base Compound of Formula (I), Form I was confirmed by XRPD (Figure 25, Table 44) and further supported by DSC (Figure 26), indicating the crystalline compound having an onset of melt at about 84.4 °C (71.9 J/g). TGA of the crystalline free base exhibited about 0.6% of weight loss due to solvent/H_2O.

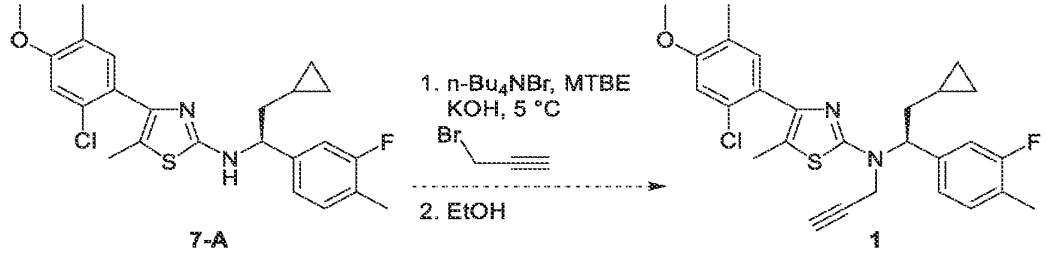
Table 44. XRPD Peak Data for the Compound of Formula (I) Crystalline Free Base Form I

2-Theta (°)	Height (cps)
5.901(15)	1221(101)
10.367(11)	1280(103)
11.762(13)	1377(107)
12.582(11)	1591(115)
13.802(2)	7326(247)
14.1541(16)	20179(410)
15.173(14)	449(61)
15.854(7)	2906(156)
16.746(5)	5113(206)
18.366(7)	1171(99)
19.586(2)	27789(481)
20.100(4)	10759(299)
20.794(4)	5441(213)
21.730(5)	7125(244)
22.239(7)	10370(294)
23.056(11)	3482(170)
23.714(7)	2300(138)
24.115(7)	8402(265)
25.666(4)	26173(467)
26.296(6)	1505(112)
26.752(4)	9919(288)
27.264(7)	1016(92)
27.874(7)	2092(132)
28.623(3)	10560(297)
29.546(6)	5811(220)
30.025(3)	2248(137)
30.737(10)	1333(105)
31.017(19)	1406(108)
31.588(10)	2292(138)
31.809(8)	2212(136)
32.126(13)	593(70)
33.200(16)	839(84)
33.613(13)	2996(158)

2-Theta (°)	Height (cps)
33.914(13)	1156(98)
34.276(16)	1008(92)
34.564(12)	1056(94)
35.397(18)	816(82)
36.073(10)	1928(127)
36.67(3)	562(68)
37.347(9)	1553(114)
37.776(12)	1573(114)
39.070(7)	1890(125)
39.743(15)	1042(93)
40.643(9)	2808(153)
41.106(8)	1107(96)
41.984(11)	2686(150)
42.376(16)	986(91)
42.901(16)	492(64)
43.543(10)	4744(199)
44.419(16)	2810(153)

Example 15B

Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), seed batch)



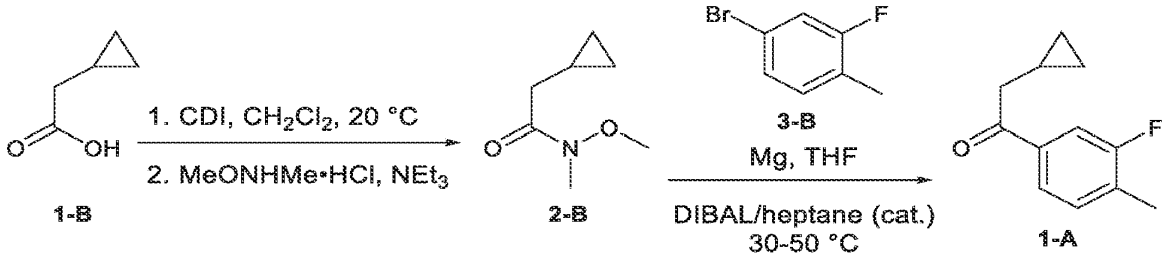
A mixture of MTBE, *tetra*-n-butylammonium bromide, and Compound 7-A cooled to 0 °C is treated with aqueous potassium hydroxide and propargyl bromide maintaining the temperature at 0 – 5 °C. The resulting biphasic mixture is aged 23 h at 4 – 6 °C. Subsequently, water and MTBE are added and the aqueous layer is discharged. The organic layer is washed twice with water and once with aqueous acetic acid at 20 °C. Ethanol is added and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol at 35 – 40 °C with a target volume of each cycle remaining in the vessel, except for the third cycle where the mixture is concentrated to dryness. Ethanol is added to the vessel and the mixture heated at 60 °C external for 0.5 h before it is cooled to 20

°C in 1 h and aged 18 h affording a suspension. The suspension is cooled to 0 °C, aged 6 h, filtered, and washed twice with ethanol pre-cooled to 0 °C to afford a solid. The solid is dried at 40 °C under vacuum to afford the compound of Formula (I).

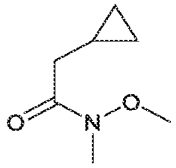
Example 15C

Scheme 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)

Scheme 2



Step 1: Preparation of 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (Compound 2-B)

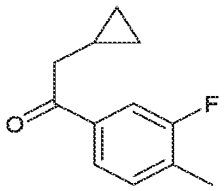


Compound 2-B

A suspension of 1,1'-Carbonyldiimidazole (152.6 kg, 1.01 eq.) in DCM (682 kg, 513 L, 7.3 w/w relative to 2-cyclopropylacetic acid) was treated with a solution of 2-cyclopropylacetic acid (1-B, 93.6 kg, 1 eq.) in DCM (248 kg, 186 L, 2.65 w/w) over at least 1 h, keeping the temperature ≤ 25 °C and compensating for significant effervescence. The resulting mixture is stirred for 15 min at 22 °C and then *N,O*-dimethylhydroxylamine•HCl (93.3 kg, 1.03 eq.) is added in portions, keeping the temperature ≤30 °C. Subsequently, triethylamine (46.4 kg, 0.49 eq.) is added to the stirring mixture at 20 - 25 °C. The resulting mixture is stirred at 22 °C at least 1 h. The mixture is washed once with $KHSO_4$ solution (0.24 M, 357.1 kg, 0.09 eq.), once with $KHSO_4$ solution (0.40 M, 365.4 kg, 0.15 eq.), once with $KHSO_4$ solution (0.80 M, 384.5 kg, 0.30 eq.), and once with $NaHCO_3$ solution (0.60 M, 393.1 kg, 0.24 eq.). Residual DCM is removed by three put-and-takes of THF (166.6 kg, 1.78 w/w) and vacuum distillation (50 – 60 °C, to minimum volume/until distillation stops). THF (333.2 kg. 3.56 w/w) is added and the yield is determined by correcting for the LOD and GC-

FID purity of the sample (131.5 kg, 98.2% corrected). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ: -0.01 – 0.03 (m, 2H) 0.32 – 0.36 (m, 2H) 0.81 – 0.90 (br m, 1H) 2.18 (d, *J*=6.80 Hz, 2H) 2.97 (s, 3 H) 3.53 (s, 3H). ESI-MS: 144.0 $[M+H]^+$.

Step 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)



Compound 1-A

Mg (turnings, 28.6 kg, 1.37 eq.) are suspended in THF (244.7 kg, 2.0 w/w) and DIBAL-H (1 M in *n*-heptane, 18.9 kg, 0.03 eq.) is added dropwise at 30 °C, The resulting mixture is stirred at 30 °C for at least 10 min and then 4-bromo-2-fluoro-1-methylbenzene (3-B, neat, 21.1 kg, 0.13 eq.) is added over at least 30 min at 30 – 50 °C. Subsequently, the mixture is treated with a solution of 4-bromo-2-fluoro-1-methylbenzene (3-B, 191.6 kg, 1.18 eq.) in THF (414.5 kg, 3.37 w/w) at 30 – 50 °C over 3 h or less. The mixture is stirred at 30 °C for at least 1 h. Subsequently, the mixture is treated with 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (2-B, 123.0 kg, 1 eq., 25.9% w/w solution in THF) over at least 1 h at 15 – 25 °C. The resulting mixture is stirred at 20 – 25 °C for at least 1 h. The stirring mixture is then treated with aqueous HCl (3 M, 10.3% w/w, 668.9 kg, 2.24 eq.) at 10 - 25 °C and the resulting mixture is stirred at least 2 h (check pH 3.0 – 3.5). The layers are separated, and the aqueous layer is combined with heptane (290.3 kg, 2.36 w/w). The layers are separated, and the organic layer is washed once with $NaHCO_3$ solution (0.63 M, 211.6 kg, 0.15 eq.) and once with NaCl solution (2.57 M, 213.0 kg, 0.55 eq.). The residual solvents are removed by vacuum distillation at 58 - 62 °C until distillation stops and then one put-and-take of toluene (275.5 kg, 2.24 w/w) at 107 – 117 °C until distillation stops. Toluene (275.5 kg, 2.24 w/w) is added and the yield is determined by correcting for the LOD and GC-FID purity of the sample (150.7 kg, 91.3% corrected). ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.07 - 0.21 (m, 2 H) 0.40 - 0.54 (m, 2 H) 1.02 (ttt, *J*=8.16, 8.16, 6.68, 6.68, 4.86, 4.86 Hz, 1 H) 2.30 (d, *J*=1.77 Hz, 3 H) 2.91 (d, *J*=6.57 Hz, 2 H) 7.44 (t, *J*=7.83 Hz, 1 H) 7.57 - 7.78 (m, 2 H). ESI-MS: 193.1 $[M+H]^+$.

Example 16: Compound of Formula (I) Crystalline Tosylate Salt Form 1

Approximately 20 mg of the Compound of Formula (I) was weighed into a vial. Using a positive displacement pipette, 250 µL of solvent (IPA) was added to the vial along with a stir bar. The vial was placed in an aluminum block on a Reacti-Therm mixer and heated to 60 °C for ~1 hour. A molar equivalent of para-toluenesulfonic acid was added to the vial (20 µL of a 2M solution in water) and allowed to stir. The sample was slow cooled back to room temperature along with mild Nitrogen gas for evaporation. Precipitate was collected, left to dry overnight, and then analyzed by XRPD, DSC, and TGA.

The crystallinity of the crystalline tosylate form 1 was confirmed by XRPD (Figure 27, Table 45) and further supported by DSC (Figure 28), indicating the crystalline compound having an onset of melt at about 156 °C (22.2 J/g). TGA of the crystalline compound is provided in Figure 28, and exhibited about 0.5% of weight loss due to solvent/H_2O.

Table 45. XRPD Peak Data for the Compound of Formula (I) Crystalline Tosylate Form 1

2-Theta (°)	Height (cps)
8.112(9)	957(89)
9.124(2)	12296(320)
9.471(2)	4519(194)
10.525(3)	8507(266)
11.316(3)	10211(292)
13.182(5)	6158(227)
13.494(6)	1598(115)
14.249(9)	2197(135)
15.208(9)	1746(121)
15.711(7)	1437(109)
16.252(5)	5723(218)
16.692(3)	3848(179)
17.540(4)	1578(115)
19.031(6)	6774(238)
19.265(4)	6491(233)
19.499(10)	3152(162)
20.401(3)	8581(267)
20.656(4)	3040(159)
21.142(3)	11498(310)
21.703(6)	4979(204)
21.870(11)	5331(211)
22.277(5)	3701(176)
22.769(3)	10159(291)

2-Theta (°)	Height (cps)
23.297(3)	14954(353)
23.532(4)	3597(173)
23.810(3)	9590(283)
24.73(2)	2325(139)
25.47(4)	1704(119)
26.087(5)	2413(142)
26.71(3)	422(59)
27.210(6)	1648(117)
27.593(5)	2825(153)
28.472(4)	6417(231)
29.51(3)	1423(109)
29.98(3)	849(84)
30.63(6)	1262(103)
30.77(3)	1121(97)
31.577(3)	5563(215)
32.74(4)	874(85)
33.73(4)	1111(96)
34.415(13)	2054(131)
34.799(11)	706(77)
35.139(15)	1320(105)
35.682(16)	1028(93)
38.39(4)	751(79)
39.743(17)	1790(122)
40.219(16)	762(80)
41.23(3)	925(88)
43.16(3)	1540(113)
44.288(12)	1142(98)

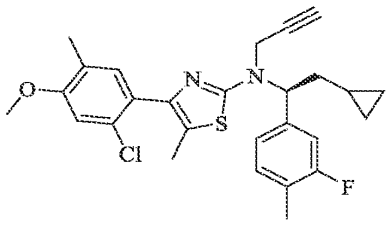
OTHER EMBODIMENTS

It is to be understood that the foregoing description is intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

2. The pharmaceutical composition of claim 1, comprising about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

3. The pharmaceutical composition of claim 1, comprising about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

4. The pharmaceutical composition of claim 1, comprising about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

5. The pharmaceutical composition of any one of claims 1-4, comprising an oily phase vehicle.

6. The pharmaceutical composition of any one of claims 1-5, comprising about 1 wt% to about 50 wt% of the oily phase vehicle.

7. The pharmaceutical composition of any one of claims 1-5, comprising about 20 wt% to about 50 wt% of the oily phase vehicle.

8. The pharmaceutical composition of any one of claims 1-5, comprising about 35 wt% to about 45 wt% of the oily phase vehicle.

9. The pharmaceutical composition of any one of claims 1-5, comprising about 39 wt% of the oily phase vehicle.

10. The pharmaceutical composition of any one of claims 1-9, wherein the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

11. The pharmaceutical composition of any one of claims 1-10, wherein the oily phase vehicle is medium-chain triglycerides.

12. The pharmaceutical composition of any one of claims 10-11, wherein the medium-chain triglycerides are Labrafac TM Lipophile WL1349.

13. The pharmaceutical composition of any one of claims 10-11, wherein the medium-chain triglycerides are Miglyol 812N.

14. The pharmaceutical composition of any one of claims 1-13, comprising an emulsifying agent.

15. The pharmaceutical composition of any one of claims 1-14, comprising about 5 wt% to about 50 wt% of the emulsifying agent.

16. The pharmaceutical composition of any one of claims 1-14, comprising about 10 wt% to about 30 wt% of the emulsifying agent.

17. The pharmaceutical composition of any one of claims 1-14, comprising about 15 wt% to about 25 wt% of the emulsifying agent.

18. The pharmaceutical composition of any one of claims 1-14, comprising about 20 wt% of the emulsifying agent.

19. The pharmaceutical composition of any one of claims 1-18, wherein the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

20. The pharmaceutical composition of any one of claims 1-19, wherein the emulsifying agent is propylene glycol dicaprylate/dicaprate.

21. The pharmaceutical composition of any one of claims 19-20, wherein the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

22. The pharmaceutical composition of any one of claims 1-21, comprising a nonionic surfactant.

23. The pharmaceutical composition of any one of claims 1-22, comprising about 5 wt% to about 50 wt% of the nonionic surfactant.

24. The pharmaceutical composition of any one of claims 1-22, comprising about 10 wt% to about 30 wt% of the nonionic surfactant.

25. The pharmaceutical composition of any one of claims 1-22, comprising about 15 wt% to about 25 wt% of the nonionic surfactant.

26. The pharmaceutical composition of any one of claims 1-22, comprising about 19 wt% of the nonionic surfactant.

27. The pharmaceutical composition of any one of claims 1-26, wherein the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides.

28. The pharmaceutical composition of any one of claims 1-27, wherein the nonionic surfactant is lauroyl polyoxyl-32 glycerides.

29. The pharmaceutical composition of any one of claims 27-28, wherein the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.

30. The pharmaceutical composition of any one of claims 1-29, comprising a solubilizing agent.

31. The pharmaceutical composition of any one of claims 1-30, comprising about 1 wt% to about 50 wt% of the solubilizing agent.

32. The pharmaceutical composition of any one of claims 1-30, comprising about 1 wt% to about 20 wt% of the solubilizing agent.

33. The pharmaceutical composition of any one of claims 1-30, comprising about 5 wt% to about 15 wt% of the solubilizing agent.

34. The pharmaceutical composition of any one of claims 1-30, comprising about 11 wt% of the solubilizing agent.

35. The pharmaceutical composition of any one of claims 1-34, wherein the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer.

36. The pharmaceutical composition of any one of claims 1-35, wherein the solubilizing agent is vitamin E polyethylene glycol succinate.

37. The pharmaceutical composition of any one of claims 35-36, wherein the vitamin E polyethylene glycol succinate is Kolliphor® TPGS.

38. The pharmaceutical composition of any one of claims 35-36, wherein the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.

39. The pharmaceutical composition of claim 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) an oily phase vehicle;

(c) an emulsifying agent;

(d) a nonionic surfactant; and

(e) a solubilizing agent.

40. The pharmaceutical composition of claim 1, comprising:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 35 wt% to about 45 wt% of an oily phase vehicle;

(c) about 15 wt% to about 25 wt% of an emulsifying agent;

(d) about 15 wt% to about 25 wt% of a nonionic surfactant; and

(e) about 5 wt% to about 15 wt% of a solubilizing agent.

41. The pharmaceutical composition of claim 1, comprising:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 39 wt% of an oily phase vehicle;

(c) about 20 wt% of an emulsifying agent;

(d) about 19 wt% of a nonionic surfactant; and

(e) about 11 wt% of a solubilizing agent.

42. The pharmaceutical composition of claim 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) a medium-chain triglycerides component;

(c) a propylene glycol dicaprylate/dicaprate component;

(d) a lauroyl polyoxyl-32 glycerides component; and

(e) a vitamin E polyethylene glycol succinate component.

43. The pharmaceutical composition of claim 1, comprising:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) about 35 wt% to about 45 wt% of medium-chain triglycerides;

(c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;

(d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and

(e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.

44. The pharmaceutical composition of claim 1, comprising:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) about 39 wt% of medium-chain triglycerides;

(c) about 20 wt% of propylene glycol dicaprylate/dicaprate;

(d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and

(e) about 11 wt% of vitamin E polyethylene glycol succinate.

45. The pharmaceutical composition of any one of claims 1-44, wherein the compound of Formula (I), or pharmaceutically acceptable salt thereof, is in crystalline form.

46. The pharmaceutical composition of any one of claims 1-45, comprising the compound of Formula (I) as a free base.

47. The pharmaceutical composition of claim 45, wherein the crystalline form comprises Form I of the compound of Formula (I).

48. The pharmaceutical composition of any one of claims 1-47, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg, based on the weight of the free base.

49. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg, based on the weight of the free base.

50. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg, based on the weight of the free base.

51. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg, based on the weight of the free base.

52. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg, based on the weight of the free base.

53. The pharmaceutical composition of any one of claims 1-52, that is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

54. The pharmaceutical composition of any one of claims 48-53, wherein the pharmaceutical composition is in tablet form.

55. The pharmaceutical composition of any one of claims 48-53, wherein the pharmaceutical composition is in capsule form.

56. The pharmaceutical composition of any one of claims 48-55, wherein the dosage form is coated.

57. A method for preparing the pharmaceutical composition of any one of claims 1-56, comprising:

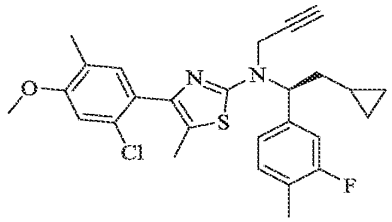
(a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;

(b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and

(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

58. The method of claim 57, further comprising:
(d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and
(e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

59. A pharmaceutical composition in oral solution dosage form comprising:
(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;
(b) one or more of a sweetener, an anti-oxidant, and a flavor; and
(c) a liquid vehicle.

60. The pharmaceutical composition of claim 59, comprising about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

61. The pharmaceutical composition of claim 59, comprising about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

62. The pharmaceutical composition of claim 59, comprising about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

63. The pharmaceutical composition of any one of claims 59-62, comprising a sweetener.

64. The pharmaceutical composition of any one of claims 59-63, comprising about 0.01 w/v% to about 1.5 w/v% of the sweetener.

65. The pharmaceutical composition of any one of claims 59-63, comprising about 0.1 w/v% to about 0.5 w/v% of the sweetener.

66. The pharmaceutical composition of any one of claims 59-63, comprising about 0.15 w/v% of the sweetener.

67. The pharmaceutical composition of any one of claims 59-66, wherein the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and avantame.

68. The pharmaceutical composition of any one of claims 59-67, wherein the sweetener is saccharin.

69. The pharmaceutical composition of any one of claims 59-68, comprising an anti-oxidant.

70. The pharmaceutical composition of any one of claims 59-69, comprising about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant.

71. The pharmaceutical composition of any one of claims 59-69, comprising about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant.

72. The pharmaceutical composition of any one of claims 59-69, comprising about 0.17 w/v% of the anti-oxidant.

73. The pharmaceutical composition of any one of claims 59-72, wherein the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid.

74. The pharmaceutical composition of any one of claims 59-73, wherein the anti-oxidant is butylated hydroxytoluene.

75. The pharmaceutical composition of any one of claims 59-74, comprising a flavor.

76. The pharmaceutical composition of any one of claims 59-75, comprising about 0.01 w/v% to about 0.5 w/v% of the flavor.

77. The pharmaceutical composition of any one of claims 59-75, comprising about 0.05 w/v% to about 0.2 w/v% of the flavor.

78. The pharmaceutical composition of any one of claims 59-75, comprising about 0.10 w/v% of the flavor.

79. The pharmaceutical composition of any one of claims 59-78, wherein the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetrarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor.

80. The pharmaceutical composition of any one of claims 59-79, wherein the flavor is FONA orange flavor.

81. The pharmaceutical composition of any one of claims 59-80, comprising about 50 w/v% to about 99.9 w/v% of the liquid vehicle.

82. The pharmaceutical composition of any one of claims 59-80, comprising about 92 w/v% to about 97 w/v% of the liquid vehicle.

83. The pharmaceutical composition of any one of claims 59-80, comprising about 94.6 w/v% of the liquid vehicle.

84. The pharmaceutical composition of any one of claims 59-83, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

85. The pharmaceutical composition of any one of claims 59-84, wherein the liquid vehicle is medium-chain triglycerides.

86. The pharmaceutical composition of any one of claims 84-85, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

87. The pharmaceutical composition of any one of claims 59-86, further comprising a surfactant.

88. The pharmaceutical composition of claim 87, comprising about 1 w/v% to about 50 w/v% of the surfactant.

89. The pharmaceutical composition of claim 87, comprising about 10 w/v% to about 30 w/v% of the surfactant.

90. The pharmaceutical composition of claim 87, comprising about 20 w/v% of the surfactant.

91. The pharmaceutical composition of any one of claims 87-90, wherein the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters.

92. The pharmaceutical composition of any one of claims 87-91, wherein the surfactant is oleoyl polyoxyl-6 glycerides.

93. The pharmaceutical composition of any one of claims 91-92, wherein the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

94. The pharmaceutical composition of any one of claims 59-93, comprising about 70 w/v% to about 80 w/v% of the liquid vehicle.

95. The pharmaceutical composition of any one of claims 59-93, comprising about 75 w/v% of the liquid vehicle.

96. The pharmaceutical composition of any one of claims 59-95, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

97. The pharmaceutical composition of any one of claims 59-96, wherein the liquid vehicle is medium-chain triglycerides.

98. The pharmaceutical composition of any one of claims 95-96, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

99. The pharmaceutical composition of claim 59, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) a sweetener;

(c) an anti-oxidant;

(d) a flavor; and

(e) a liquid vehicle.

100. The pharmaceutical composition of claim 99, further comprising a surfactant.

101. The pharmaceutical composition of claim 59, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;

(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;

(d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and

(e) about 92 w/v% to about 97 w/v% of a liquid vehicle.

102. The pharmaceutical composition of claim 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of a sweetener;

(c) about 0.17 w/v% of an anti-oxidant;

(d) about 0.1 w/v% of a flavor; and

(e) about 94.6 w/v% of a liquid vehicle.

103. The pharmaceutical composition of claim 59, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;

(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;

(d) about 0.05 w/v% to about 0.2 w/v% of a flavor;

(e) about 15 w/v% to about 25 w/v% of a surfactant; and

(f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

104. The pharmaceutical composition of claim 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of a sweetener;

(c) about 0.17 w/v% of an anti-oxidant;

(d) about 0.1 w/v% of a flavor;

(e) about 20 w/v% of a surfactant; and

(f) about 75 w/v% of a liquid vehicle.

105. The pharmaceutical composition of claim 59, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) saccharin;

(c) butylated hydroxytoluene;

(d) FONA orange flavor; and

(e) medium-chain triglycerides.

106. The pharmaceutical composition of claim 105, further comprising oleoyl polyoxyl-6 glycerides.

107. The pharmaceutical composition of claim 106, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;

(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;

(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and

(e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

108. The pharmaceutical composition of claim 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of saccharin;

(c) about 0.17 w/v% of butylated hydroxytoluene;

(d) about 0.1 w/v% of FONA orange flavor; and

(e) about 94.6 w/v% of medium-chain triglycerides.

109. The pharmaceutical composition of claim 59, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-

2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;

(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;

(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;

(e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and

(f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

110. The pharmaceutical composition of claim 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of saccharin;

(c) about 0.17 w/v% of butylated hydroxytoluene;

(d) about 0.1 w/v% of FONA orange flavor;

(e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and

(f) about 75 w/v% of medium-chain triglycerides.

111. The pharmaceutical composition of any one of claims 59-110, comprising the compound of Formula (I) as a free base.

112. The pharmaceutical composition of any one of claims 59-111, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base.

113. The pharmaceutical composition of claim 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base.

114. The pharmaceutical composition of claim 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg/mL, based on the weight of the free base.

115. The pharmaceutical composition of claim 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg/mL, based on the weight of the free base.

116. The pharmaceutical composition of any one of claims 1-56, having a viscosity between about 15 to about 40 centipoise at about 45 °C.

117. A method for preparing the pharmaceutical composition of any one of claims 59-116, comprising:

(a) mixing a liquid vehicle with a sweetener;

(b) mixing the mixture of step (a) with an anti-oxidant and a flavor;

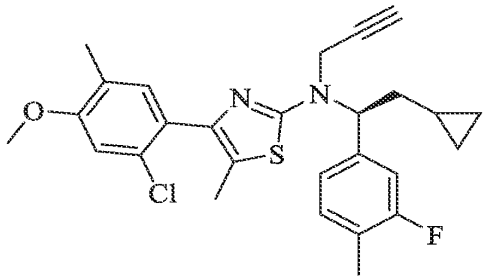
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and

(d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

118. The method of claim 117, wherein step (a) comprises mixing a liquid vehicle with a sweetener and a surfactant.

119. A spray-dried dispersion comprising:

a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and

a polymer selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer;

wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:1 to about 1:9.

120. The spray-dried dispersion of claim 119, wherein the neutral polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

121. The spray-dried dispersion of claim 119, wherein the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer.

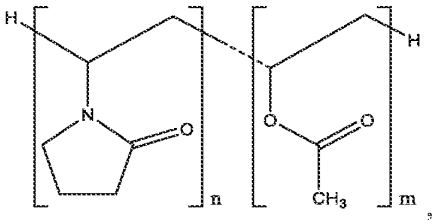
122. The spray-dried dispersion of claim 119, wherein the pyrrolidone polymer is selected from polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone vinyl acetate (PVP/VA).

123. The spray-dried dispersion of claim 122, wherein the pyrrolidone polymer is PVP/VA.

124. The spray-dried dispersion of claim 123, wherein the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 40:60 to about 60:40 by weight.

125. The spray-dried dispersion of claim 124, wherein the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight.

126. The spray-dried dispersion of any one of claims 122-125, wherein the copolymer has the structure:

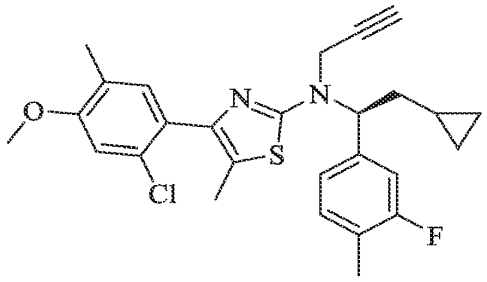


wherein the value of n is about 1 to about 2 times the value of m.

127. The spray-dried dispersion of claim 126, wherein the copolymer is copovidone, wherein the value of n is about 1.16 times the value of m.

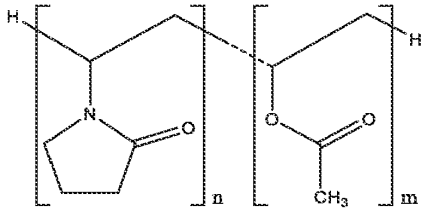
128. The spray-dried dispersion of claim 126, wherein the copolymer is copovidone having an average molecular weight of about 45,000 to about 70,000.

129. A spray-dried dispersion comprising:
a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and
a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



, wherein the value of n is about 1 to about 2 times the value of m and the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight; and
wherein the weight ratio of the compound of Formula (I) to the copolymer is from about 1:1 to about 1:9.

130. The spray-dried dispersion of any one of claims 119-129, wherein the compound of Formula (I) and the polymer together form homogeneous particles.

131. The spray-dried dispersion of any one of claims 119-130, wherein the particles have a particle size distribution D_{50} of about 5 μm to about 100 μm.

132. The spray-dried dispersion of any one of claims 119-131, wherein the particles have a particle size distribution D_{50} of about 10 μm to about 50 μm.

133. The spray-dried dispersion of any one of claims 119-132, wherein the particles have a particle size distribution D_{50} of about 15 μm to about 30 μm.

134. The spray-dried dispersion of any one of claims 119-133, wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:1.5 to about 1:9.

135. The spray-dried dispersion of any one of claims 119-134, wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:2.5 to about 1:4.

136. The spray-dried dispersion of any one of claims 119-135, wherein the weight ratio of the compound of Formula (I) to the polymer is about 1:3.

137. The spray-dried dispersion of any one of claims 119-136, wherein the particles have a residual solvent content less than about 2 wt %.

138. The spray-dried dispersion of any one of claims 119-137, wherein the particles have a residual solvent content less than about 1 wt %.

139. The spray-dried dispersion of any one of claims 119-138, wherein the particles have a residual solvent content of about 0.5 wt % or less.

140. The spray-dried dispersion of any one of claims 119-139, wherein the compound of Formula (I) in the dispersion is substantially amorphous.

141. A pharmaceutical composition comprising the spray-dried dispersion of any one of claims 119-140 and one or more pharmaceutically acceptable excipients.

142. The pharmaceutical composition of claim 141, wherein the spray-dried dispersion is present in an amount of about 20% to about 90% w/w of the composition.

143. The pharmaceutical composition of claim 142, wherein the spray-dried dispersion is present in an amount of about 40% to about 80% w/w of the composition.

144. The pharmaceutical composition of claim 141, wherein the spray-dried dispersion is present in an amount of about 1% to about 20% w/w of the composition.

145. The pharmaceutical composition of claim 144, wherein the spray-dried dispersion is present in an amount of about 13% w/w of the composition.

146. The pharmaceutical composition of any one of claims 141-145, wherein the pharmaceutical excipients are selected from the group consisting of a filler, a lubricant, and combinations thereof.

147. The pharmaceutical composition of claim 146, wherein the filler is selected from the group consisting of a binder, a diluent, a disintegrant, a glidant, a surfactant, and combinations thereof.

148. The pharmaceutical composition of any one of claims 141-147 formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg.

149. The pharmaceutical composition of claim 148, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg.

150. The pharmaceutical composition of claim 149, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg.

151. The pharmaceutical composition of claim 149, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg.

152. The pharmaceutical composition of any one of claims 141-151, wherein the pharmaceutical excipients are selected from the group consisting of a glidant, a filler, a disintegrant, a lubricant, and a combination thereof.

153. The pharmaceutical composition of any one of claims 141-152, comprising a glidant.

154. The pharmaceutical composition of any one of claims 152-153, comprising about 0.1 w/w% to about 5 w/w% of the glidant.

155. The pharmaceutical composition of any one of claims 152-153, comprising about 0.1 w/w% to about 1 w/w% of the glidant.

156. The pharmaceutical composition of any one of claims 152-153, comprising about 0.67 w/w% of the glidant.

157. The pharmaceutical composition of any one of claims 152-156, wherein the glidant is selected from calcium silicate, silicon dioxide, and talc.

158. The pharmaceutical composition of any one of claims 152-157, wherein the glidant is calcium silicate.

159. The pharmaceutical composition of any one of claims 141-158, comprising a filler.

160. The pharmaceutical composition of any one of claims 152-159, comprising about 30 w/w% to about 99 w/w% of the filler.

161. The pharmaceutical composition of any one of claims 152-159, comprising about 50 w/w% to about 90 w/w% of the filler.

162. The pharmaceutical composition of any one of claims 152-159, comprising about 75.5 w/w% of the filler.

163. The pharmaceutical composition of any one of claims 152-162, wherein the filler is selected from mannitol, microcrystalline cellulose, lactose, starch, isomalt, silicified microcrystalline cellulose, Dicalcium Phosphate, maltodextrin, and a combination thereof.

164. The pharmaceutical composition of any one of claims 152-163, wherein the filler is a combination of mannitol and microcrystalline cellulose.

165. The pharmaceutical composition of any one of claims 163-164, comprising about 30 w/w% to about 80 w/w% of mannitol.

166. The pharmaceutical composition of any one of claims 163-164, comprising about 50 w/w% to about 60 w/w% of mannitol.

167. The pharmaceutical composition of any one of claims 163-164, comprising about 56 w/w% of mannitol.

168. The pharmaceutical composition of any one of claims 163-167, comprising about 1 w/w% to about 50 w/w% of microcrystalline cellulose.

169. The pharmaceutical composition of any one of claims 163-167, comprising about 10 w/w% to about 30 w/w% of microcrystalline cellulose.

170. The pharmaceutical composition of any one of claims 163-167, comprising about 20 w/w% of microcrystalline cellulose.

171. The pharmaceutical composition of any one of claims 163-167, comprising about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose.

172. The pharmaceutical composition of any one of claims 141-171, comprising a disintegrant.

173. The pharmaceutical composition of any one of claims 152-172, comprising about 1 w/w% to about 30 w/w% of the disintegrant.

174. The pharmaceutical composition of any one of claims 152-172, comprising about 5 w/w% to about 15 w/w% of the disintegrant.

175. The pharmaceutical composition of any one of claims 152-172, comprising about 10 w/w% of the disintegrant.

176. The pharmaceutical composition of any one of claims 152-175, wherein the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, and sodium bicarbonate.

177. The pharmaceutical composition of any one of claims 152-176, wherein the disintegrant is croscarmellose sodium.

178. The pharmaceutical composition of any one of claims 141-177, comprising a lubricant.

179. The pharmaceutical composition of any one of claims 152-178, comprising about 0.1 w/w% to about 10 w/w% of the lubricant.

180. The pharmaceutical composition of any one of claims 152-178, comprising about 0.1 w/w% to about 1 w/w% of the lubricant.

181. The pharmaceutical composition of any one of claims 152-178, comprising about 0.5 w/w% of the lubricant.

182. The pharmaceutical composition of any one of claims 152-181, wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid, sodium lauryl sulfate, sodium oleate, glyceryl behenate, and talc.

183. The pharmaceutical composition of any one of claims 152-182, wherein the lubricant is sodium stearyl fumarate.

184. The pharmaceutical composition of any one of claims 141-183, comprising:
(a) the spray-dried dispersion of any one of claims 119-140;
(b) a glidant;
(c) a filler; and
(d) a disintegrant.

185. The pharmaceutical composition of any one of claims 141-183, comprising:
(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of any one of claims 119-140;
(b) about 0.1 w/w% to about 1 w/w% of a glidant;

(c) about 50 w/w% to about 90 w/w% of a filler; and

(d) about 5 w/w% to about 0.2 w/w% of a disintegrant.

186. The pharmaceutical composition of any one of claims 141-183, comprising:

(a) about 13 w/w% of the spray-dried dispersion of any one of claims 119-140;

(b) about 0.67 w/w% of a glidant;

(c) about 75.5 w/w% of a filler; and

(d) about 10 w/w% of a disintegrant.

187. The pharmaceutical composition of any one of claims 141-183, comprising:

(a) the spray-dried dispersion of Example 3;

(b) calcium silicate;

(c) a combination of mannitol and microcrystalline cellulose; and

(d) croscarmellose sodium.

188. The pharmaceutical composition of claim 187, comprising:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of Example 3;

(b) about 0.1 w/w% to about 1 w/w% of calcium silicate;

(c) about 50 w/w% to about 60 w/w% of mannitol and about 10 w/w% to about 30 w/w% of microcrystalline cellulose; and

(d) about 5 w/w% to about 0.2 w/w% of croscarmellose sodium.

189. The pharmaceutical composition of claim 188, comprising:

(a) about 13 w/w% of the spray-dried dispersion of Example 3;

(b) about 0.67 w/w% of calcium silicate;

(c) about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose; and

(d) about 10 w/w% of croscarmellose sodium.

190. The pharmaceutical composition of any one of claims 141-189 that is formulated as a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

191. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in tablet form.

192. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in capsule form.

193. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in sachet form.

194. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in granule form.

195. The pharmaceutical composition of any one of claims 190-192, wherein the pharmaceutical composition is coated.

196. A method for preparing the spray-dried dispersion of any one of claims 119-140, comprising:

dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and

spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer.

197. The method of claim 196, comprising removing the organic solvent after formation of the spray-dried dispersion by drying the spray-dried dispersion.

198. The method of claim 197, wherein the spray-dried dispersion is dried with a convection tray dryer.

199. The method of any one of claims 196-198, wherein the organic solvent is acetone.

200. The method of any one of claims 196-199, wherein the spray dryer inlet temperature is about 60°C to about 80°C.

201. The method of claim 200, wherein the spray dryer inlet temperature is about 72°C.

202. The method of any one of claims 196-201, wherein the spray dryer outlet temperature is about 25°C to about 45°C.

203. The method of claim 202, wherein the spray dryer outlet temperature is about 35°C.

204. The method of any one of claims 196-203, wherein the homogeneous particles comprise a bulk density of less than about 0.2 g/mL.

205. The method of claim 204, wherein the homogeneous particles comprise a bulk density of less than about 0.15 g/mL.

206. The method of any one of claims 196-205, wherein the homogeneous particles comprise a tapped density of less than about 0.3 g/mL.

207. The method of claim 206, wherein the homogeneous particles comprise a tapped density of less than about 0.25 g/mL.

208. A method for preparing a pharmaceutical composition, comprising combining the spray-dried dispersion of any one of claims 119-140 with one or more pharmaceutically acceptable excipients.

209. The method of claim 208, comprising:
(a) blending the spray-dried dispersion of any one of claims 119-140, with a glidant;
(b) further blending the blend of step (a) with a filler and a disintegrant;
(c) screening the blend of step (b) to break up aggregates and assist with blend uniformity;
(d) further blending the intragranular blend of step (c);
(e) compaction of the intragranular blend of step (d) via roller compaction to form granules; and
(f) milling of ribbon from roller compaction into granules of step (e).

210. A method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the spray-dried dispersion of any one of claims 119-140 or the pharmaceutical composition of any one of claims 141-195.

211. The method of claim 210, wherein the spray-dried dispersion or the pharmaceutical composition is administered to the subject in a fed state.

212. The method of claim 210 or claim 211, wherein the spray-dried dispersion or the pharmaceutical composition is administered to the subject with a nutritional composition.

213. The method of claim 212, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

214. The method of claim 212 or claim 213, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

215. The method of any one of claims 212-214, wherein the nutritional composition is administered within 30 minutes of administration of the spray-dried dispersion or the pharmaceutical composition.

216. The method of any one of claims 211-215, wherein administering the spray-dried dispersion or the pharmaceutical composition exhibits a positive food effect.

217. The method of claim 216, wherein the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof when comparing oral administration of the spray-dried dispersion or pharmaceutical composition in the fed and fasting states.

218. The method of any one of claims 211-217, wherein the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10.

219. The method of any one of claims 211-217, wherein the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

220. The method of any one of claims 210-219, wherein the subject is a pediatric subject.

221. A method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, comprising orally administering to the subject the pharmaceutical composition of any one of claims 141-195, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

222. The method of claim 221, wherein the subject is a pediatric subject.

223. A method of improving oral bioavailability of a compound of Formula (I) in a subject, comprising orally administering to the subject the pharmaceutical composition of any one of claims 141-195, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

224. The method of claim 223, wherein the subject is a pediatric subject.

225. The spray-dried dispersion of any one of claims 119-140, wherein the spray-dried dispersion is formulated for oral administration and exhibits a positive food effect when administered orally.

226. The spray-dried dispersion of claim 225, wherein the spray-dried dispersion has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10.

227. The spray-dried dispersion of claim 225, wherein the spray-dried dispersion has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10.

228. A crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

229. The salt of claim 228, having Form 1 of the Compound of Formula (I).

230. The salt of claim 228 or claim 229, having an X-ray powder diffraction pattern as substantially shown in Figure 27.

231. The salt of any one of claims 228-230, having a DSC thermogram substantially as depicted in Figure 28.

232. The salt of any one of claims 228-231, having a thermogravimetric analysis (TGA) thermogram substantially as depicted in Figure 28.

233. The salt of any one of claims 228-232, having at least one X-ray powder diffraction (XRPD) peak, in terms of 2-theta (± 0.2 degrees), selected 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

234. The salt of any one of claims 228-232, having at least two X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

235. The salt of any one of claims 228-232, having at least three X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

236. The salt of any one of claims 228-232, having at least four X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

237. The salt of any one of claims 228-232, having characteristic X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), at 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

238. The salt of any one of claims 228-237, having an endothermic peak having an onset of melt at about 156 °C (22.2 J/g) in a differential scanning calorimetry (DSC) thermogram.

239. A method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

240. The method of claim 239, wherein the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

241. The method of claim 240, wherein the circadian release occurs between the hours of 2 a.m. and 10 a.m.

242. The method of any one of claims 239-241, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

243. The method of any one of claims 239-242, wherein the level of 17-hydroxyprogesterone is reduced by at least 25%.

244. The method of any one of claims 239-242, wherein the level of 17-hydroxyprogesterone is reduced by at least 50%.

245. The method of any one of claims 239-244, wherein the level of adrenocorticotropic hormone is reduced by at least 25%.

246. The method of any one of claims 239-244, wherein the level of adrenocorticotropic hormone is reduced by at least 40%.

247. The method of any one of claims 239-244, wherein the level of adrenocorticotropic hormone is reduced by at least 50%.

248. The method of any one of claims 239-247, wherein the level of androstenedione is reduced by at least 25%.

249. The method of any one of claims 239-247, wherein the level of androstenedione is reduced by at least 30%.

250. The method of any one of claims 239-247, wherein the level of androstenedione is reduced by at least 50%.

251. The method of any one of claims 239-250, wherein the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

252. The method of any one of claims 239-251, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

253. The method of any one of claims 239-252, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

254. A method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia,

comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of androstenedione in the subject.

255. The method of claim 254, wherein the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

256. The method of claim 254 or 255, wherein the androstenedione is reduced by at least 25%.

257. The method of claim 254 or 255, wherein the androstenedione is reduced by at least 30%.

258. The method of claim 254 or 255, wherein the androstenedione is reduced by at least 50%.

259. A method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

260. The method of claim 259, wherein the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

261. A method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

262. The method of claim 261, wherein the corticosteroid is a glucocorticoid.

263. A method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof,
wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

264. The method of any one of claims 259-263, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

265. The method of any one of claims 259-264, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

266. The method of any one of claims 259-264, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an

amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

267. The method of any one of claims 259-266, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

268. The method of any one of claims 259-267, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

269. The method of any one of claims 259-268, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

270. A method of treating congenital adrenal hyperplasia in a subject comprising

(i)measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii)analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii)administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

271. The method of claim 270, further comprising (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i).

272. The method of claim 271, further comprising (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

273. The method of claim 271 or 272, wherein steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window.

274. The method of any one of claims 271-273, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m.

275. The method of any one of claims 271-273, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

276. The method of any one of claims 271-275, wherein steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

277. The method of any one of claims 271-275, wherein steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

278. The method of any one of claims 270-277, wherein step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

279. The method of any one of claims 270-278, wherein step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

280. The method of any one of claims 270-279, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

281. The method of any one of claims 270-279, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

282. The method of any one of claims 270-281, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

283. A method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, where in the subject is in a fed state.

284. The method of claim 283, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition.

285. The method of claim 284, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

286. The method of claim 284 or 285, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

287. The method of any one of claims 284-286, wherein the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

288. A pharmaceutical composition of any one of claims 1-56, 59-116 or 141-195 for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

289. The pharmaceutical composition for use according to claim 288, wherein the subject is in a fed state.

290. The pharmaceutical composition for use according to claim 288 or claim 289, wherein the subject is administered the pharmaceutical composition with a nutritional composition.

291. The pharmaceutical composition for use according to claim 290, wherein the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%.

292. The pharmaceutical composition for use according to claim 290, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

293. The pharmaceutical composition for use according to any one of claims 290-292, wherein the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces.

294. The pharmaceutical composition for use according to any one of claims 290-293, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

295. The pharmaceutical composition for use according to any one of claims 290-294, wherein the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

296. The pharmaceutical composition for use according to any one of claims 289-295, wherein administering the pharmaceutical composition exhibits a positive food effect.

297. The pharmaceutical composition for use according to claim 296, wherein the positive food effect is measured in terms of C_{max}, AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.

298. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

299. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

300. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

301. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

302. The pharmaceutical composition for use according to any one of claims 288-301, wherein the subject is a pediatric subject.

303. The pharmaceutical composition for use according to any one of claims 289-295, wherein the pharmaceutical composition exhibits a positive food effect when administered orally.

304. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10.

305. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1 to about 4 or about 5 to about 10.

306. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3.

307. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1.5 to about 3.

308. The pharmaceutical composition for use according to any one of claims 288-307, wherein the pharmaceutical composition is administered to the subject with a meal.

309. The pharmaceutical composition for use according to claim 308, wherein the meal is a high fat meal.

310. The pharmaceutical composition for use according to claim 308, wherein the meal is a low fat meal.

311. The pharmaceutical composition for use according to any one of claims 308-310, wherein the pharmaceutical composition is administered within about 5 minutes after the start of the meal.

312. The pharmaceutical composition for use according to any one of claims 308-311, wherein the meal is an evening meal.

313. The pharmaceutical composition for use according to any one of claims 308-311, wherein the meal is a morning meal.

314. The pharmaceutical composition for use according to any one of claims 308-313, wherein administering the pharmaceutical composition exhibits a positive food effect.

315. The pharmaceutical composition for use according to claim 314, wherein the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof of the compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.

316. The pharmaceutical composition for use according to any one of claims 308-315, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

317. The pharmaceutical composition for use according to any one of claims 308-316, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

318. The pharmaceutical composition for use according to any one of claims 308-315, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

319. The pharmaceutical composition for use according to any one of claims 308-315 or 318, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

320. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

321. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

322. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

323. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

324. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

325. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

326. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

327. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

328. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

329. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

330. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

331. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

332. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

333. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a

dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

334. The pharmaceutical composition for use according to any one of claims 288-333, wherein the subject is concurrently receiving a dose of a glucocorticoid.

335. The pharmaceutical composition for use according to claim 334, wherein the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate.

336. The pharmaceutical composition for use according to claim 334 or 335, wherein the glucocorticoid is cortisol (hydrocortisone).

337. The pharmaceutical composition for use according to claim 334 or 335, wherein the glucocorticoid is cortisone.

338. The pharmaceutical composition for use according to claim 334 or 335, wherein the glucocorticoid is prednisone.

339. The pharmaceutical composition for use according to any one of claims 334-338, wherein the glucocorticoid dose is measured in hydrocortisone equivalents.

340. The pharmaceutical composition for use according to any one of claims 334-339, wherein the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents.

341. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition.

342. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition.

343. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition.

344. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition.

345. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition

346. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

347. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

348. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid

dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

349. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

350. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

351. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

352. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

353. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

354. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

355. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.

356. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.

357. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

358. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition.

359. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotropic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

360. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotropic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

361. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotropic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

362. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotropic hormone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

363. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the pharmaceutical composition.

364. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

365. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

366. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

367. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

368. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

369. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

370. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

371. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

372. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

373. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

374. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition.

375. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

376. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

377. The pharmaceutical composition for use according to any one of claims 334-376, wherein the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition.

378. The pharmaceutical composition for use according to claim 377, wherein one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition.

379. The pharmaceutical composition for use according to any one of claims 341-378, wherein the time period of administration is at least about 4 weeks.

380. The pharmaceutical composition for use according to any one of claims 341-378, wherein the time period of administration is at least about 24 weeks.

381. The pharmaceutical composition for use according to any one of claims 341-378, wherein the time period of administration is at least about one year.

382. The pharmaceutical composition for use according to any one of claims 288-381, wherein the subject is a pediatric subject.

383. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is less than or equal to six years old.

384. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is greater than six years old and less than eleven years old.

385. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is greater than ten years old and less than fifteen years old.

386. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is greater than fourteen years old and less than nineteen years old.

387. The pharmaceutical composition for use according to any one of claims 288-381, wherein the subject is an adult subject.

388. The pharmaceutical composition for use according to any one of claims 387, wherein the adult subject is over eighteen years old.

389. The pharmaceutical composition for use according to any one of claims 288-388, wherein the subject is female.

390. The pharmaceutical composition for use according to any one of claims 288-388, wherein the subject is male.

391. The pharmaceutical composition for use according to any one of claims 288-390, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

392. The pharmaceutical composition for use according to any one of claims 288-390, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid salt of any one of claims 228-238.

393. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or a pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

394. The compound of claim 393, wherein the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during

the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

395. The compound of claim 394, wherein the circadian release occurs between the hours of 2 a.m. and 10 a.m.

396. The compound of any one of claims 393-395, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

397. The compound of any one of claims 393-396, wherein the level of 17-hydroxyprogesterone is reduced by at least 25%.

398. The compound of any one of claims 393-396, wherein the level of 17-hydroxyprogesterone is reduced by at least 50%.

399. The compound of any one of claims 393-398, wherein the level of adrenocorticotropic hormone is reduced by at least 25%.

400. The compound of any one of claims 393-398, wherein the level of adrenocorticotropic hormone is reduced by at least 40%.

401. The compound of any one of claims 393-398, wherein the level of adrenocorticotropic hormone is reduced by at least 50%.

402. The compound of any one of claims 393-401, wherein the level of androstenedione is reduced by at least 25%.

403. The compound of any one of claims 393-401, wherein the level of androstenedione is reduced by at least 30%.

404. The compound of any one of claims 393-401, wherein the level of androstenedione is reduced by at least 50%.

405. The compound of any one of claims 393-401, wherein the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

406. The compound of any one of claims 393-405, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

407. The compound of any one of claims 393-406, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

408. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound is administered in an amount sufficient to reduce the level of androstenedione in the subject.

409. The compound of claim 408, wherein the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

410. The compound of claim 408 or 409, wherein the level of androstenedione is reduced by at least 25%.

411. The compound of claim 408 or 409, wherein the level of androstenedione is reduced by at least 30%.

412. The compound of claim 408 or 409, wherein the level of androstenedione is reduced by at least 50%.

413. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

414. The compound of claim 413, wherein the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

415. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

416. The compound of claim 415, wherein the corticosteroid is a glucocorticoid.

417. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism,

hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

418. The compound of any one of claims 413-417, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

419. The compound of any one of claims 413-418, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

420. The compound of any one of claims 413-417, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

421. The compound of any one of claims 413-420, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

422. The compound of any one of claims 413-421, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-

2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

423. The compound of any one of claims 413-422, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

424. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject comprising

(i)measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

425. The compound of claim 424, further comprising (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i).

426. The compound of claim 425, further comprising (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-

methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

427. The compound of claim 425 or 426, wherein steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window.

428. The compound of any one of claims 425-427, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m.

429. The compound of any one of claims 425-427, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

430. The compound of any one of claims 425-429, wherein steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

431. The compound of any one of claims 425-429, wherein steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

432. The compound of any one of claims 424-431, wherein step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

433. The compound of any one of claims 424-432, wherein step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

434. The compound of any one of claims 424-433, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-

2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

435. The compound of any one of claims 424-433, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

436. The compound of any one of claims 424-435, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

437. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof for use in a method of treating congenital adrenal hyperplasia (CAH), in a subject, wherein the subject is in a fed state.

438. The compound of claim 437, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition.

439. The compound of claim 438, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

440. The compound of claim 438 or 439, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

441. The compound of any one of claims 438-440, wherein the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

442. The compound of any one of claims 437-441, wherein administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, exhibits a positive food effect.

443. The compound of claim 442, wherein the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof when comparing oral administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the fed and fasting states.

444. The compound of any one of claims 437-443, wherein the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10.

445. The compound of any one of claims 437-443, wherein the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

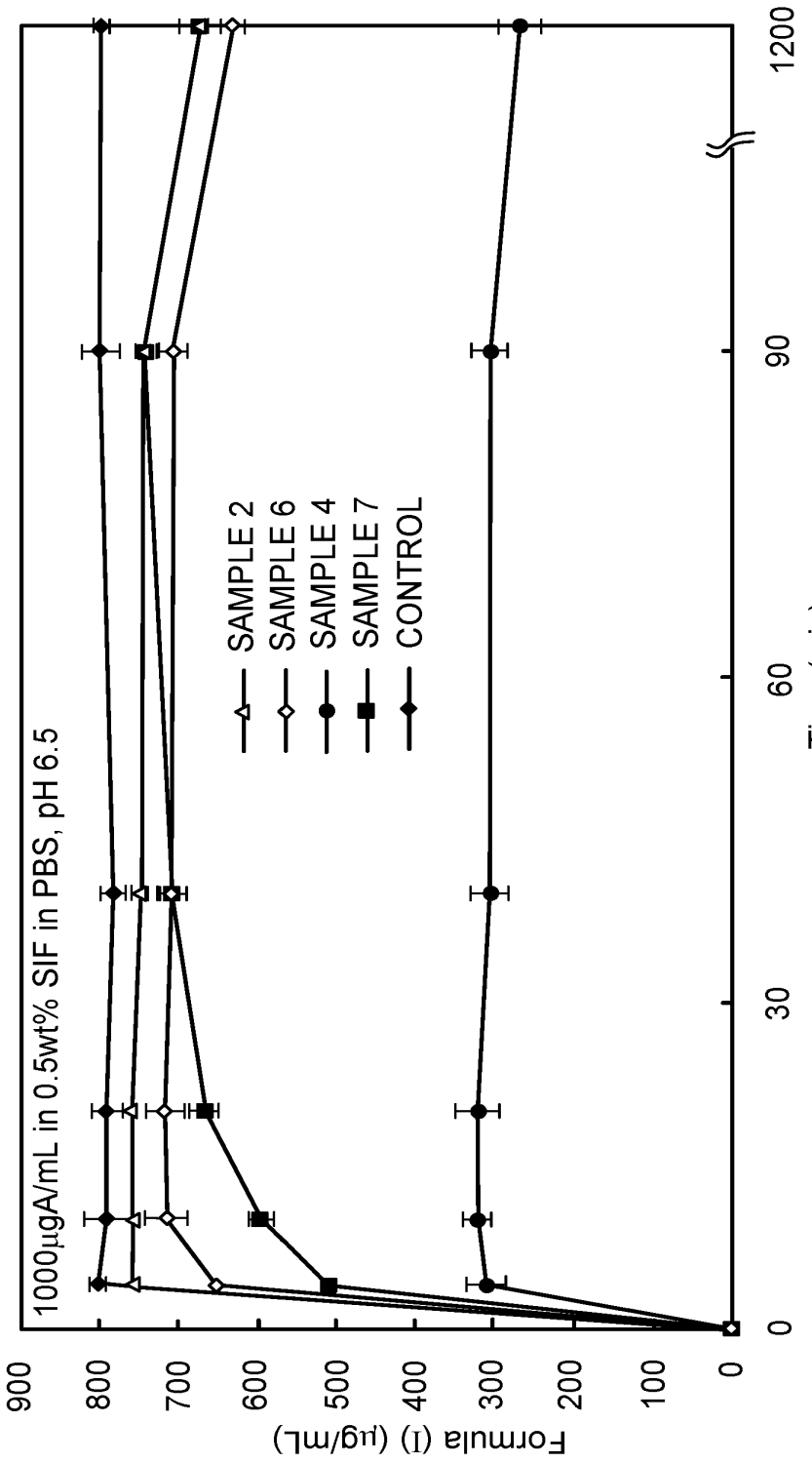

1000μgA/mL in 0.5wt% SIF in PBS, pH 6.5
SAMPLE 2
SAMPLE 6
SAMPLE 4
SAMPLE 7
CONTROL
Formula (I) (μg/mL)
Time (min)
0
100
200
300
400
500
600
700
800
900
0
30
60
90
1200

FIG. 1

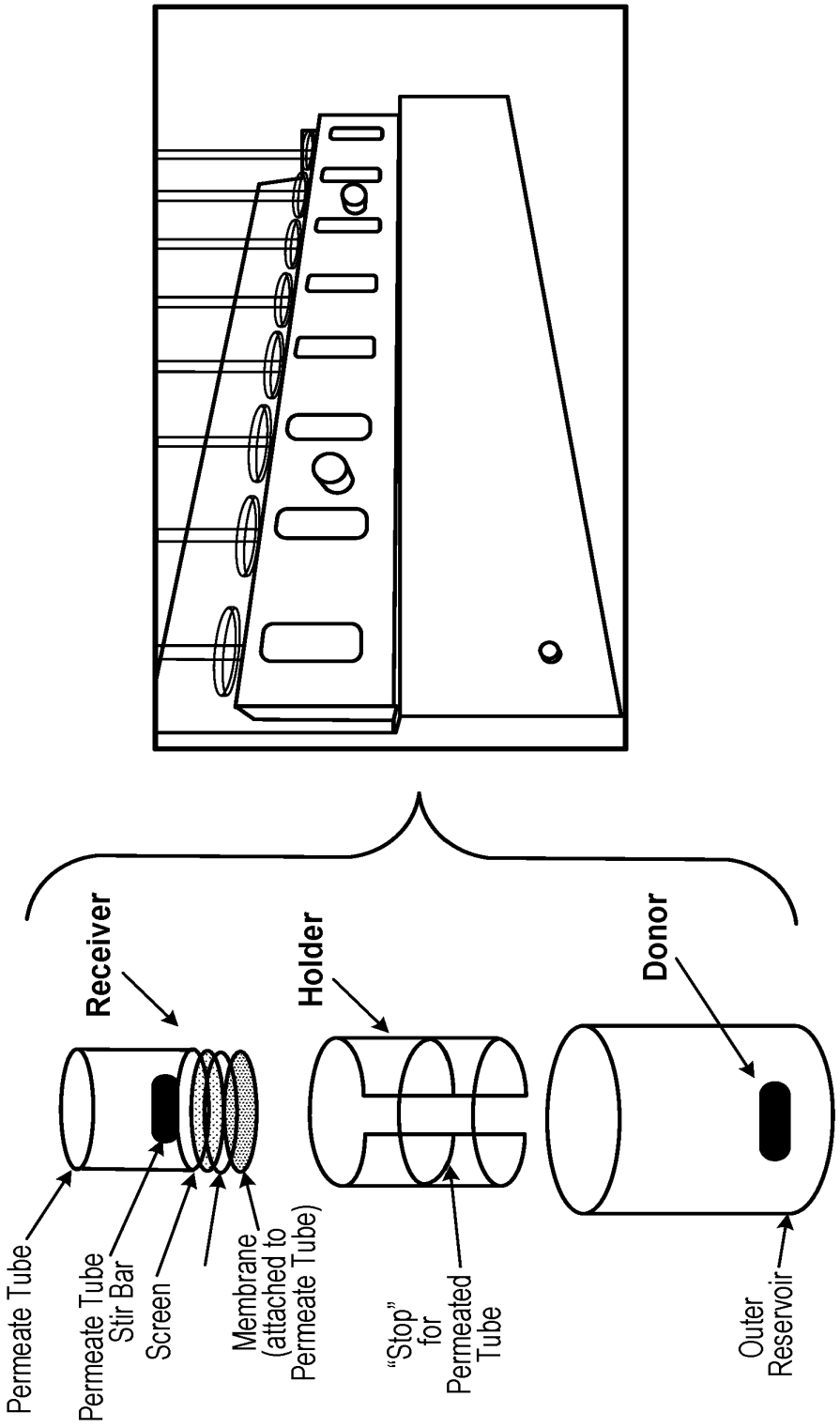

Receiver
Holder
Donor
Permeate Tube
Permeate Tube Stir Bar
Screen
Membrane (attached to Permeate Tube)
"Stop" for Permeated Tube
Outer Reservoir

FIG. 2

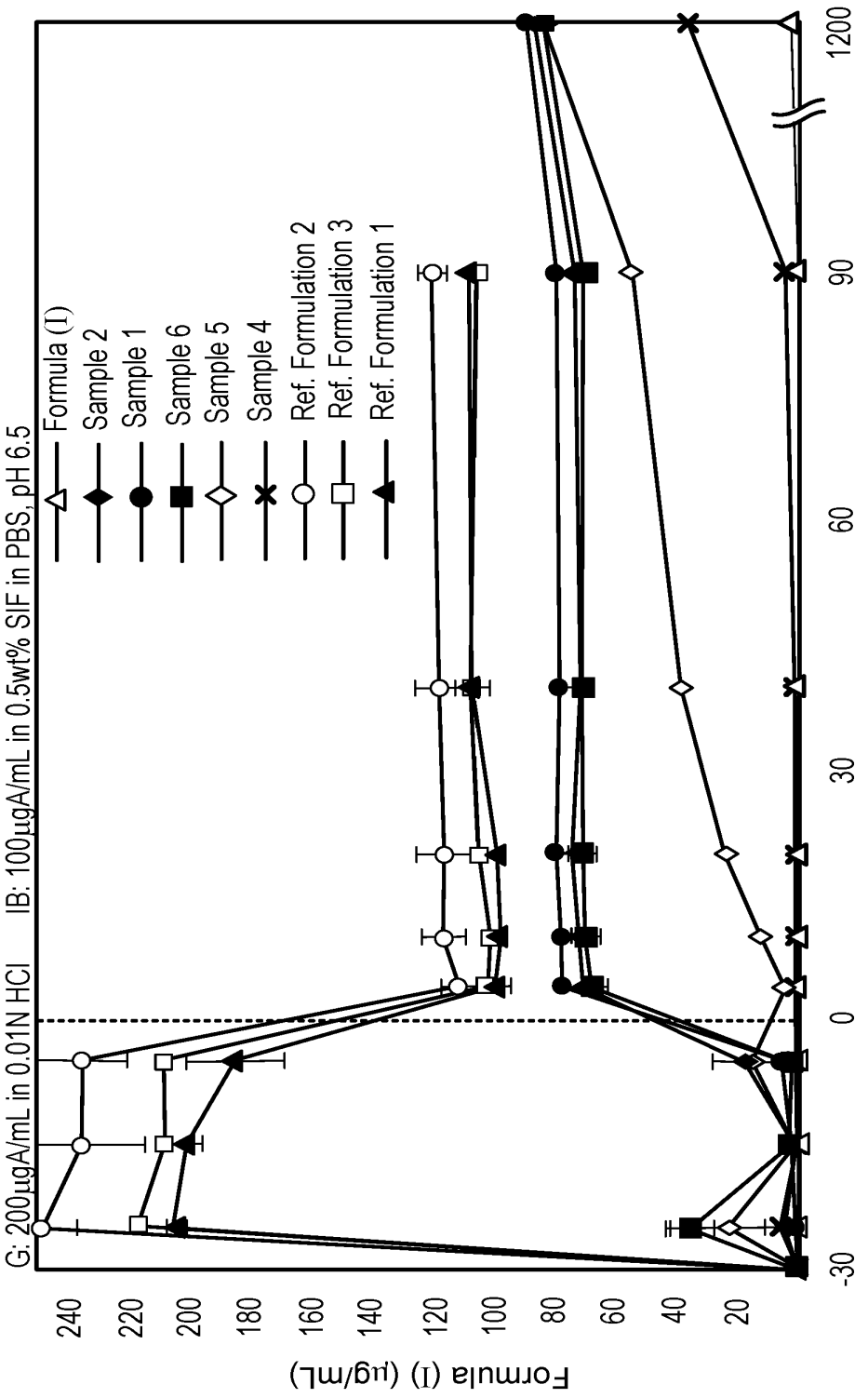

G: 200µgA/mL in 0.01N HCl IB: 100µgA/mL in 0.5wt% SIF in PBS, pH 6.5
Formula (I)
Sample 2
Sample 1
Sample 6
Sample 5
Sample 4
Ref. Formulation 2
Ref. Formulation 3
Ref. Formulation 1
Formula (I) (µg/mL)
240
220
200
180
160
140
120
100
80
60
40
20
-30
0
30
60
90
1200
Time (min)

FIG. 3

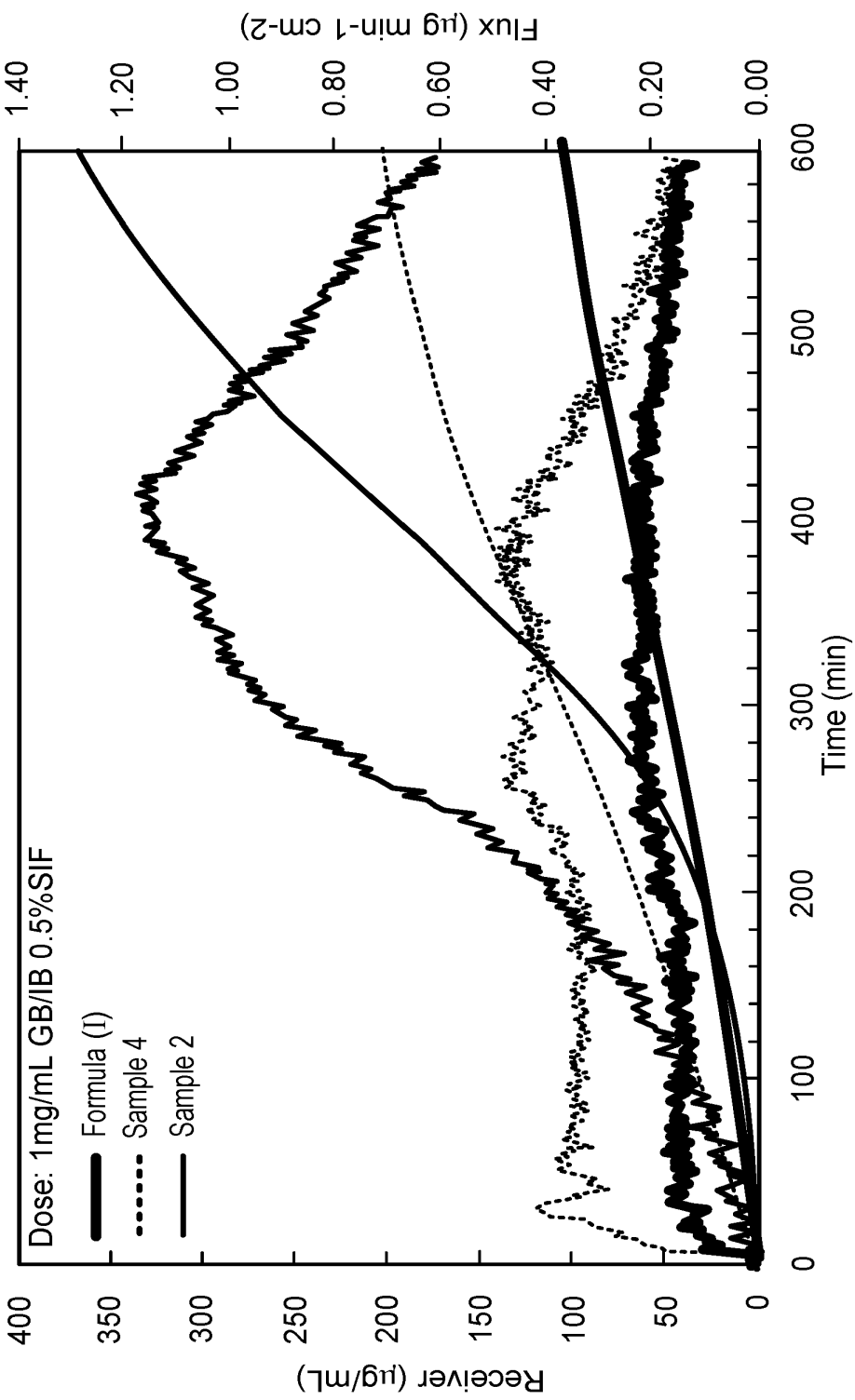

Dose: 1mg/mL GB/IB 0.5%SIF
Formula (I)
Sample 4
Sample 2
Receiver (µg/mL)
Flux (µg min-1 cm-2)
Time (min)
0
50
100
150
200
250
300
350
400
0.00
0.20
0.40
0.60
0.80
1.00
1.20
1.40
0
100
200
300
400
500
600

FIG. 4

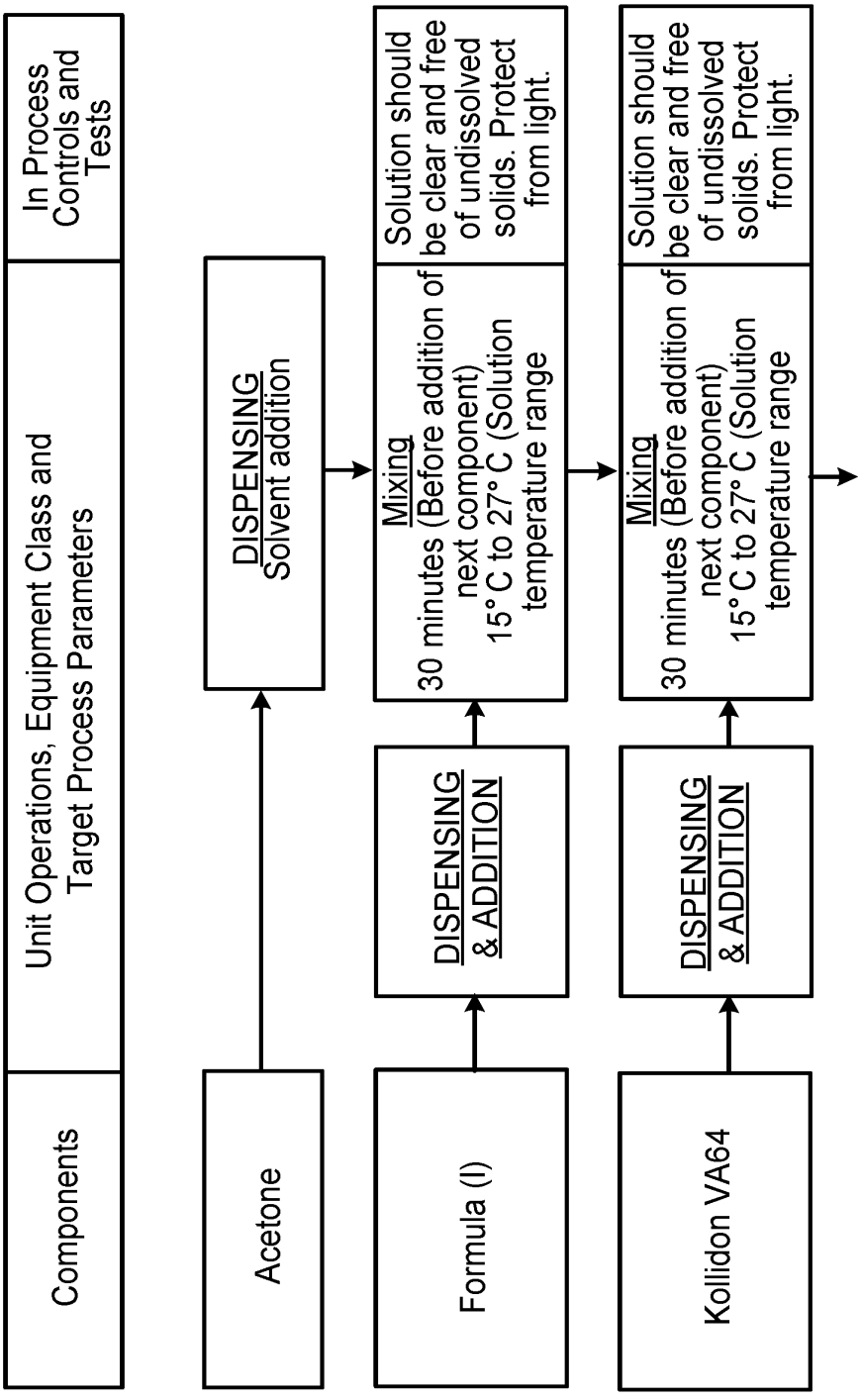

Components
Unit Operations, Equipment Class and Target Process Parameters
In Process Controls and Tests
Acetone
DISPENSING
Solvent addition
Formula (I)
DISPENSING & ADDITION
Mixing
30 minutes (Before addition of next component)
15° C to 27° C (Solution temperature range
Solution should be clear and free of undissolved solids. Protect from light.
Kollidon VA64
DISPENSING & ADDITION
Mixing
30 minutes (Before addition of next component)
15° C to 27° C (Solution temperature range
Solution should be clear and free of undissolved solids. Protect from light.

FIG. 5

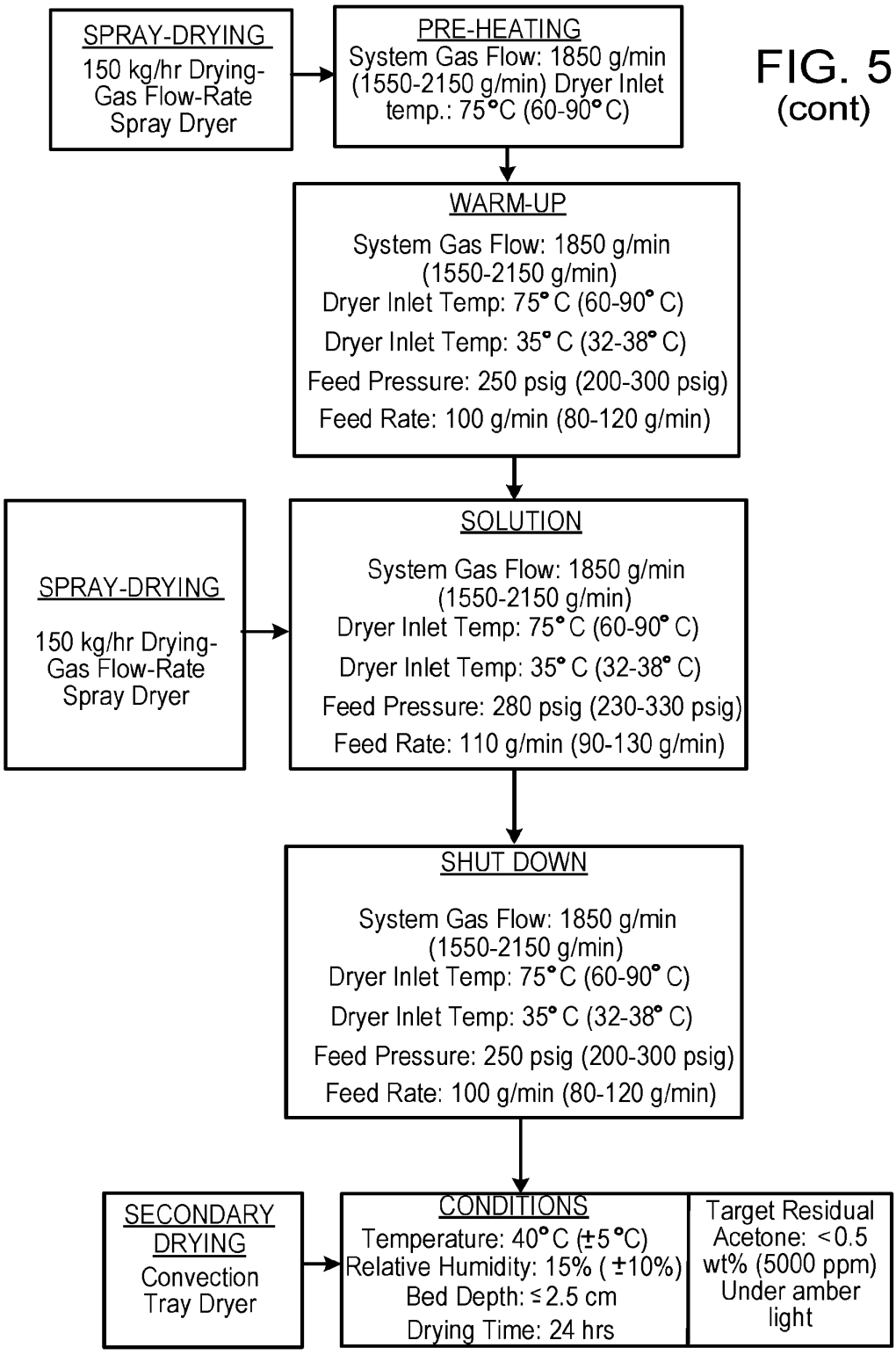

SPRAY-DRYING
150 kg/hr Drying-Gas Flow-Rate Spray Dryer
PRE-HEATING
System Gas Flow: 1850 g/min (1550-2150 g/min) Dryer Inlet temp.: 75°C (60-90° C)
WARM-UP
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 250 psig (200-300 psig)
Feed Rate: 100 g/min (80-120 g/min)
SPRAY-DRYING
150 kg/hr Drying-Gas Flow-Rate Spray Dryer
SOLUTION
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 280 psig (230-330 psig)
Feed Rate: 110 g/min (90-130 g/min)
SHUT DOWN
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 250 psig (200-300 psig)
Feed Rate: 100 g/min (80-120 g/min)
SECONDARY DRYING
Convection Tray Dryer
CONDITIONS
Temperature: 40° C (±5 °C)
Relative Humidity: 15% (±10%)
Bed Depth: ≤ 2.5 cm
Drying Time: 24 hrs
Target Residual Acetone: <0.5 wt% (5000 ppm) Under amber light

FIG. 5
(cont)

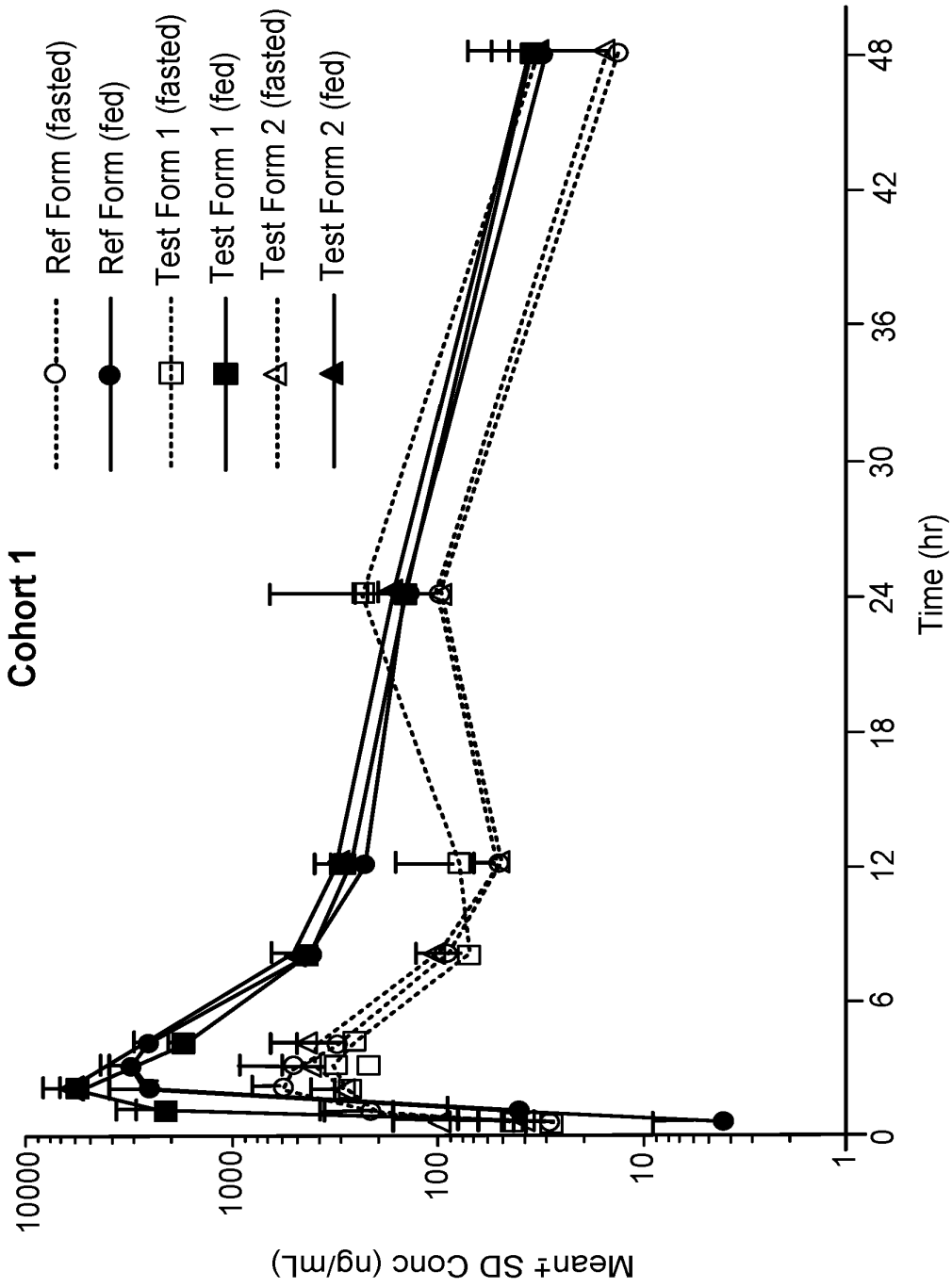

Cohort 1
Ref Form (fasted)
Ref Form (fed)
Test Form 1 (fasted)
Test Form 1 (fed)
Test Form 2 (fasted)
Test Form 2 (fed)
Mean± SD Conc (ng/mL)
10000
1000
100
10
1
0
6
12
18
24
30
36
42
48
Time (hr)

FIG. 6A

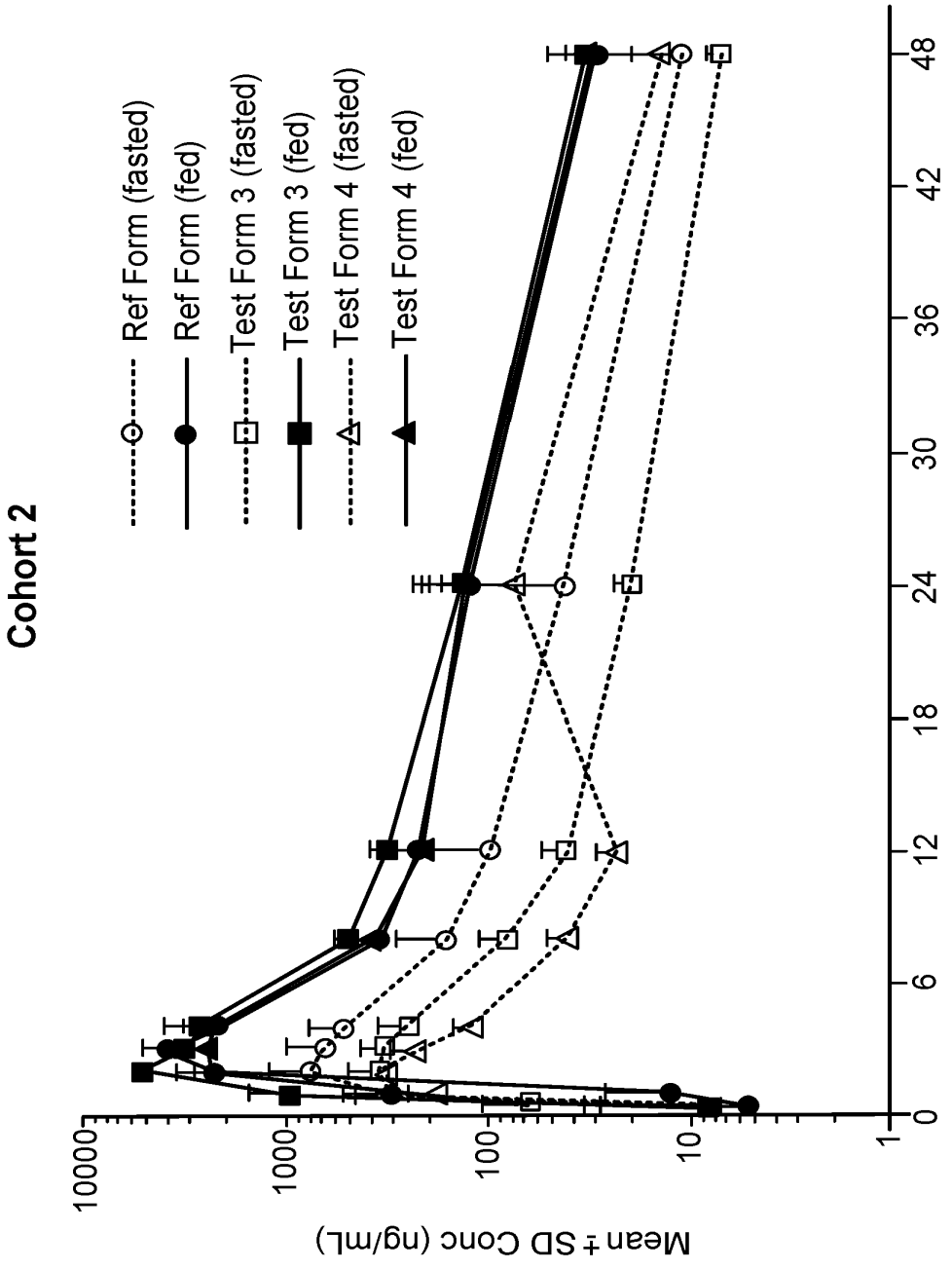

Cohort 2
Ref Form (fasted)
Ref Form (fed)
Test Form 3 (fasted)
Test Form 3 (fed)
Test Form 4 (fasted)
Test Form 4 (fed)
Mean ± SD Conc (ng/mL)
10000
1000
100
10
1
0
6
12
18
24
30
36
42
48
Time (hr)

FIG. 6B

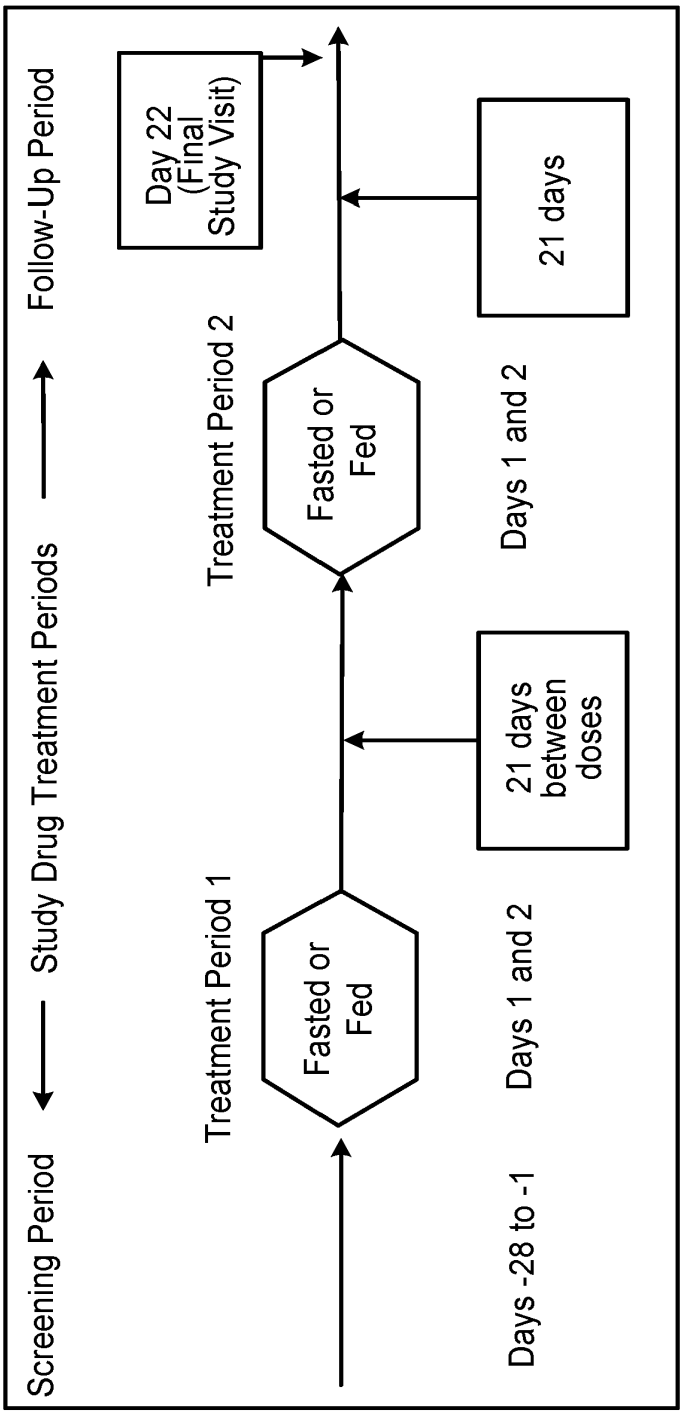

Screening Period
Study Drug Treatment Periods
Follow-Up Period
Days -28 to -1
Treatment Period 1
Fasted or Fed
Days 1 and 2
21 days between doses
Treatment Period 2
Fasted or Fed
Days 1 and 2
21 days
Day 22 (Final Study Visit)

FIG. 7

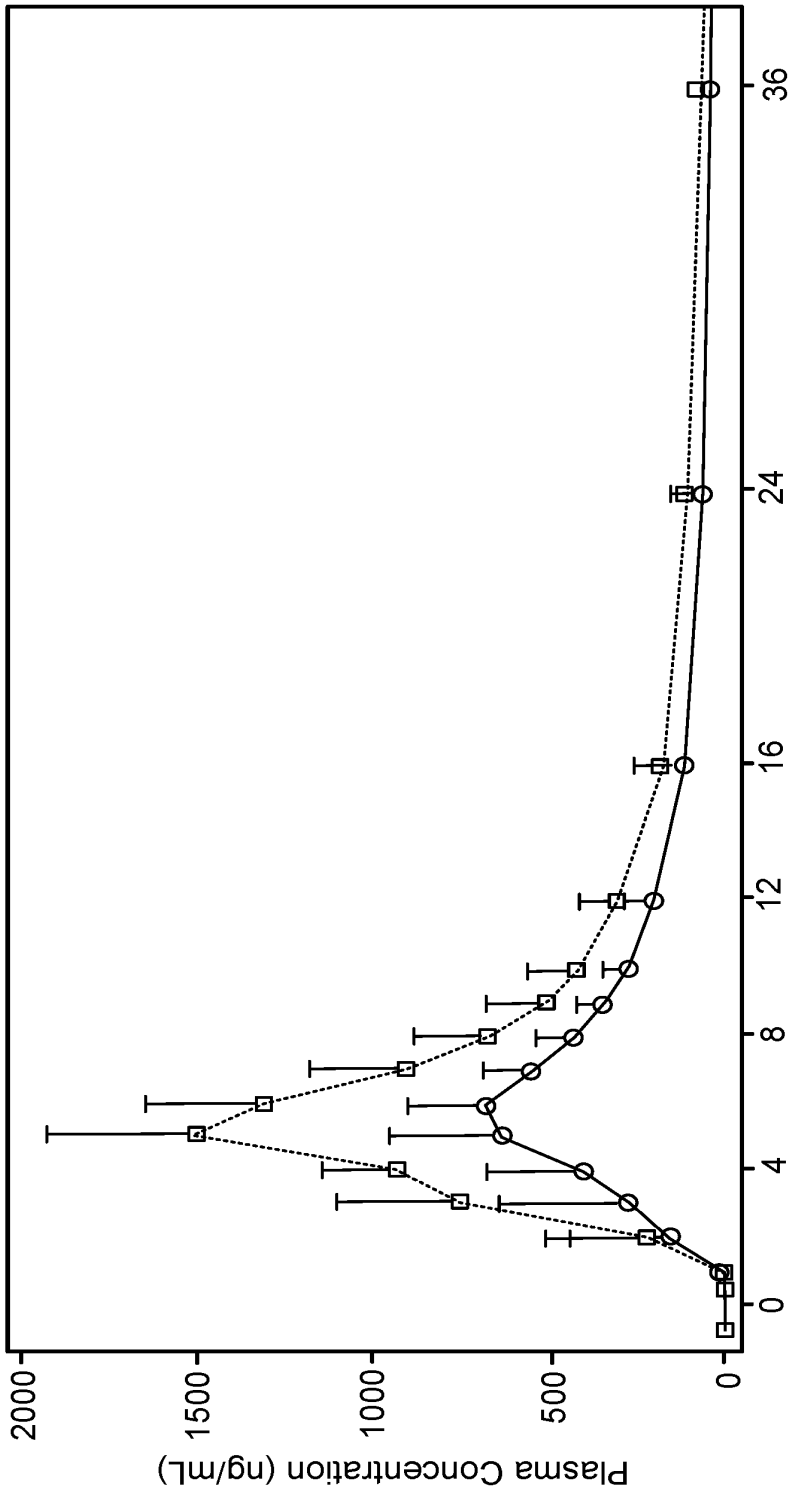

Plasma Concentration (ng/mL)
2000
1500
1000
500
0
0
4
8
12
16
24
36
Scheduled Time Postdose (Hours)
Treatment Fasted Fed

FIG. 8A

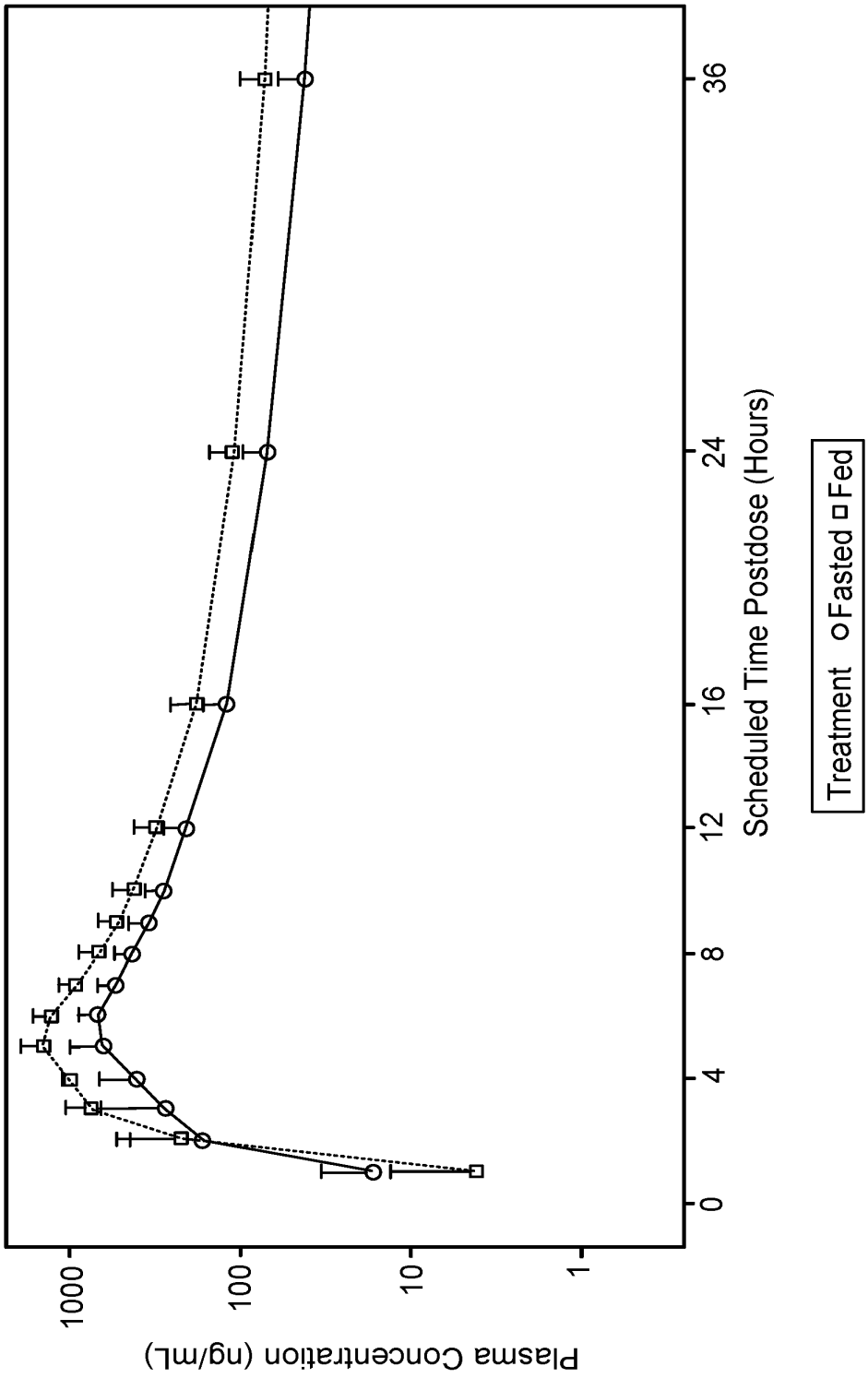

Plasma Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
24
36
Scheduled Time Postdose (Hours)
Treatment Fasted Fed

FIG. 8B

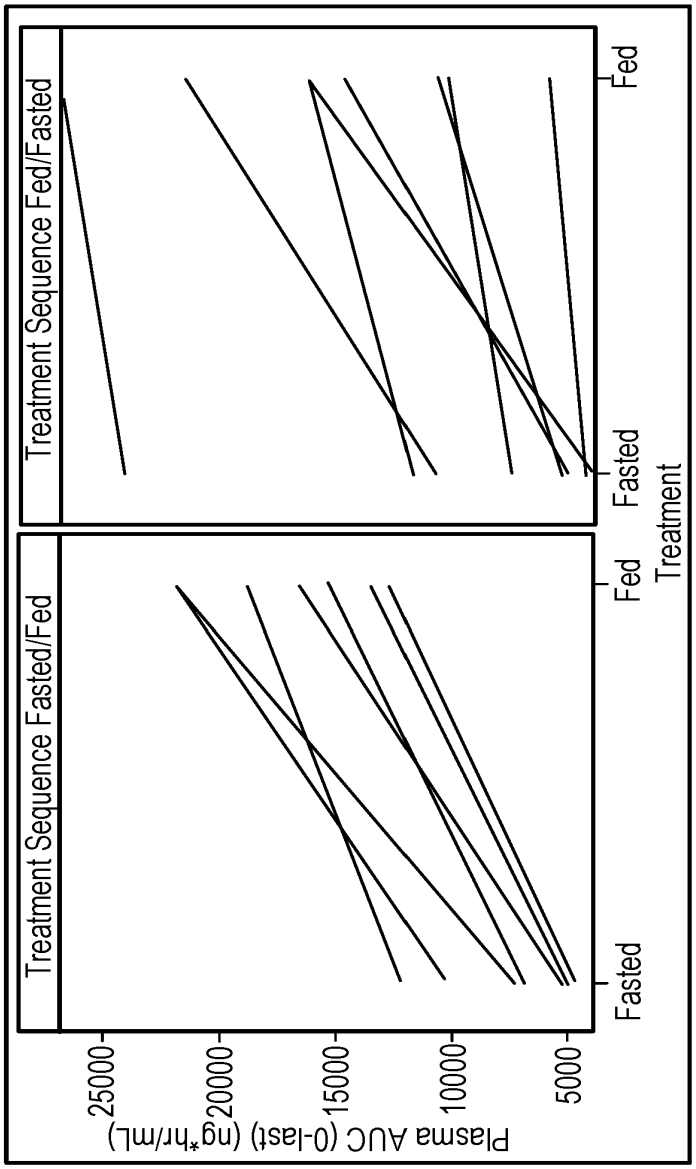

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma AUC (0-last) (ng*hr/mL)
25000
20000
15000
10000
5000
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9A

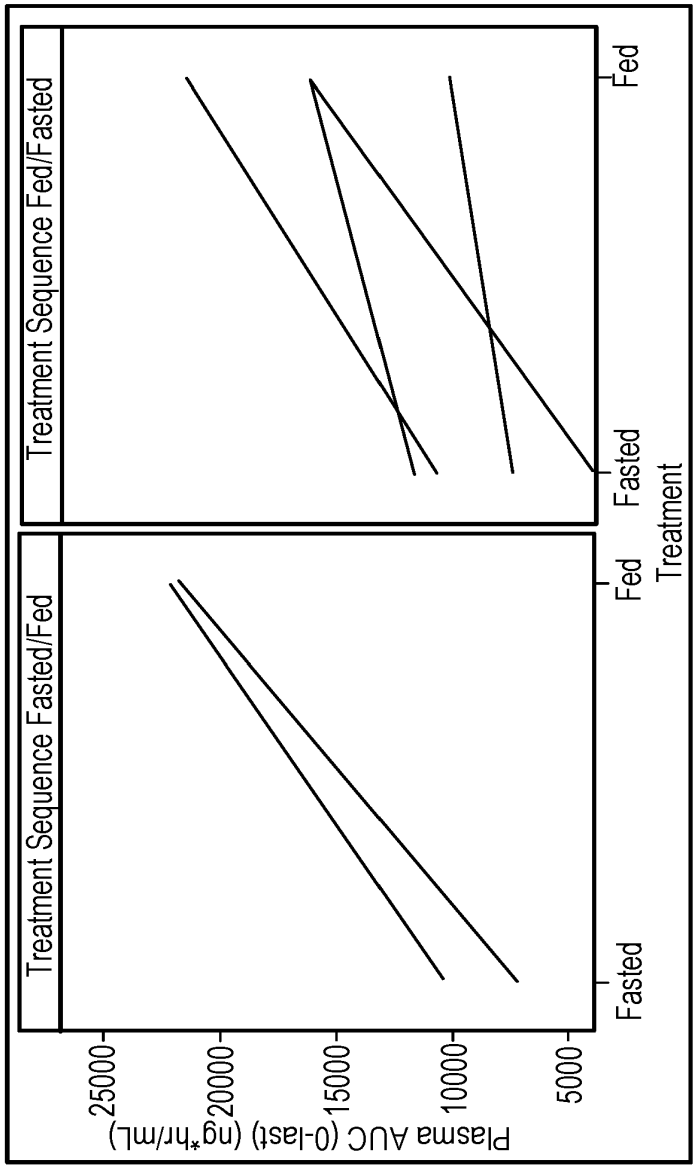

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma AUC (0-last) (ng*hr/mL)
25000
20000
15000
10000
5000
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9B

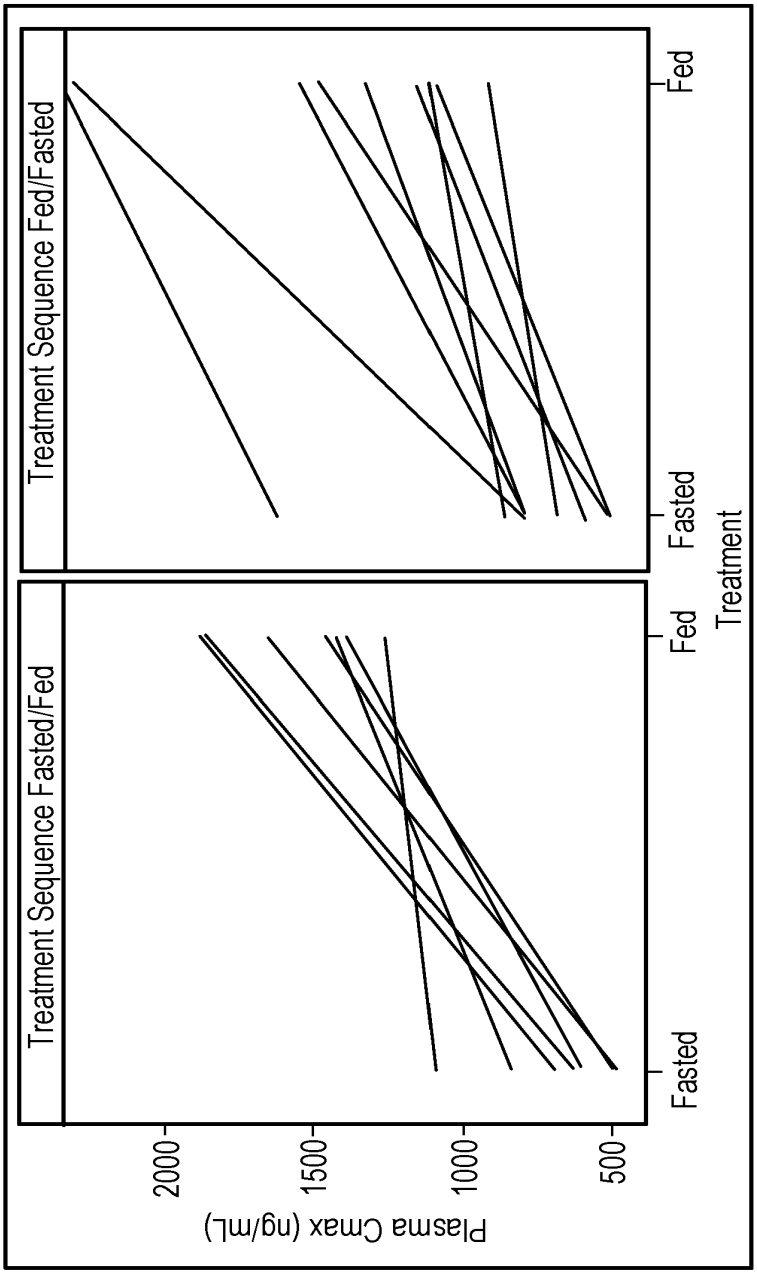
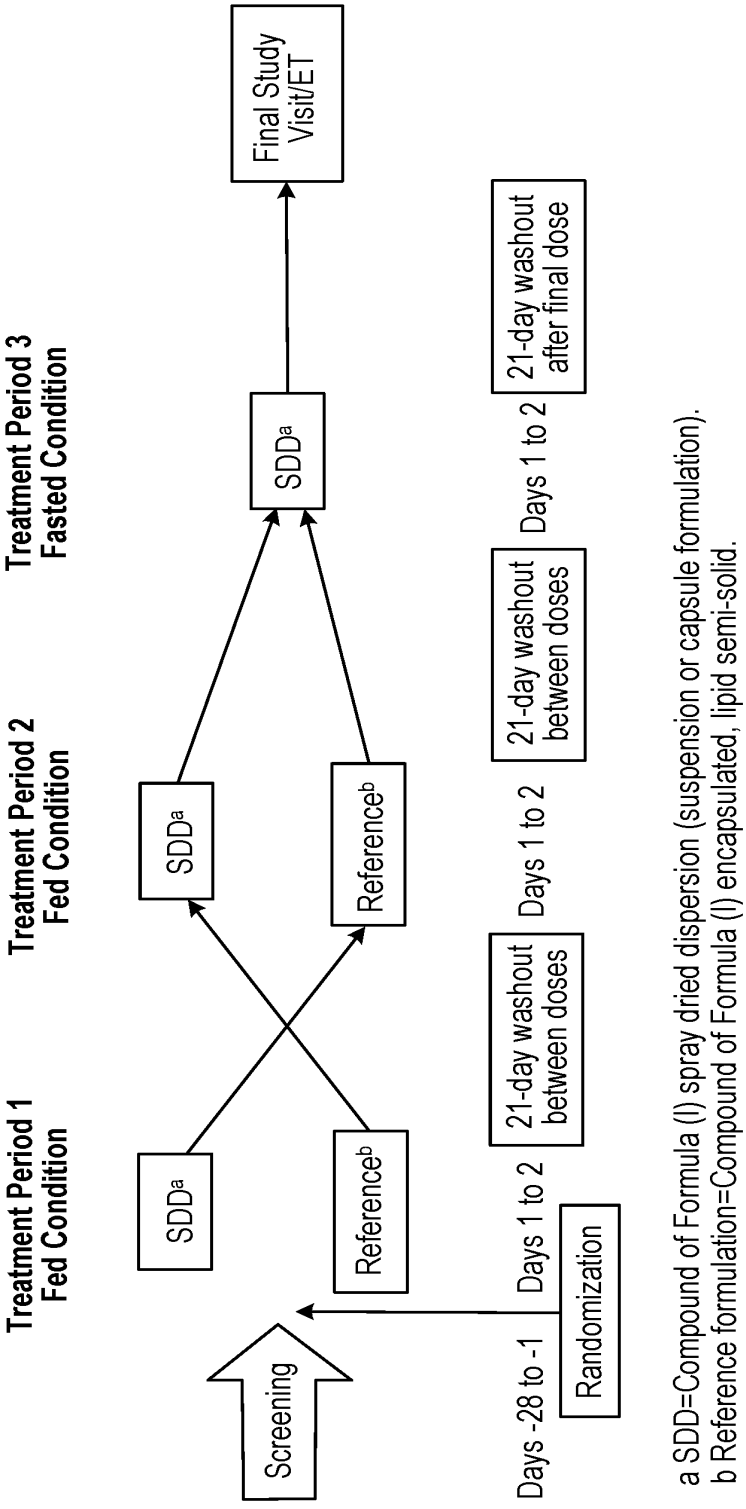

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma Cmax (ng/mL)
2000
1500
1000
500
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9C



a SDD=Compound of Formula (I) spray dried dispersion (suspension or capsule formulation).
b Reference formulation=Compound of Formula (I) encapsulated, lipid semi-solid.

FIG. 10

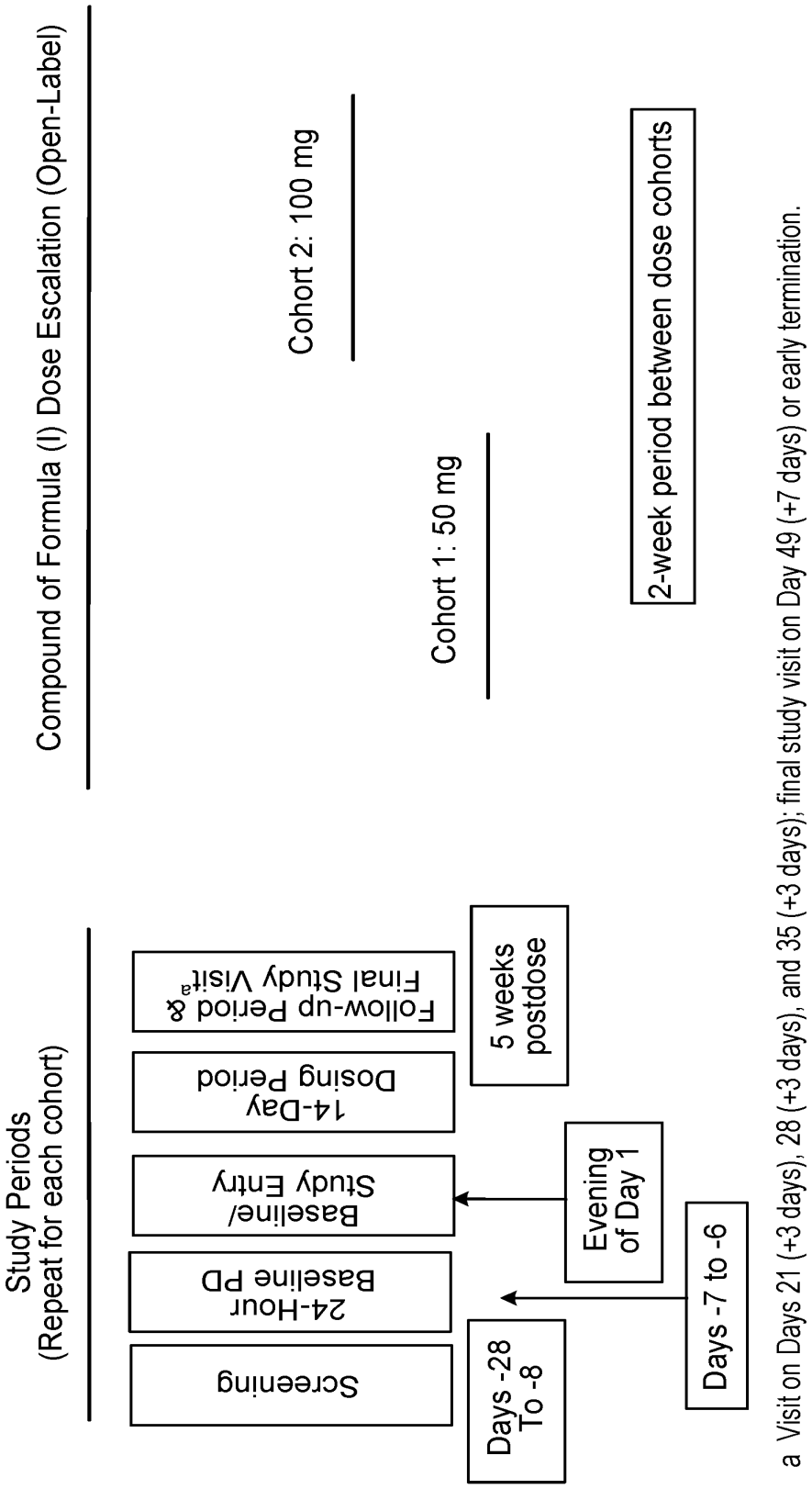


FIG. 11

a Visit on Days 21 (+3 days), 28 (+3 days), and 35 (+3 days); final study visit on Day 49 (+7 days) or early termination.
PD = pharmacodynamic.

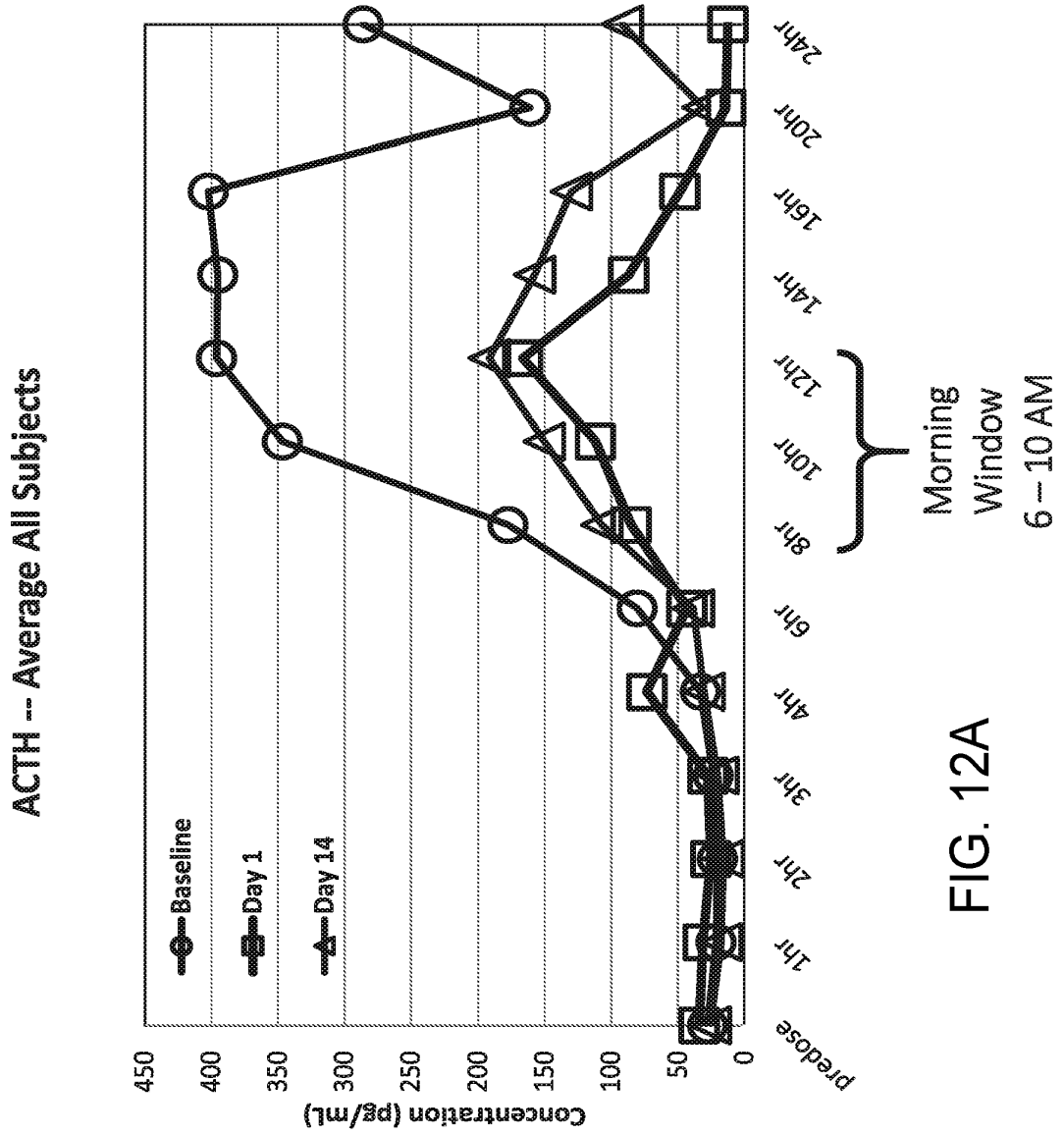

ACTH -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
450
400
350
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 12A

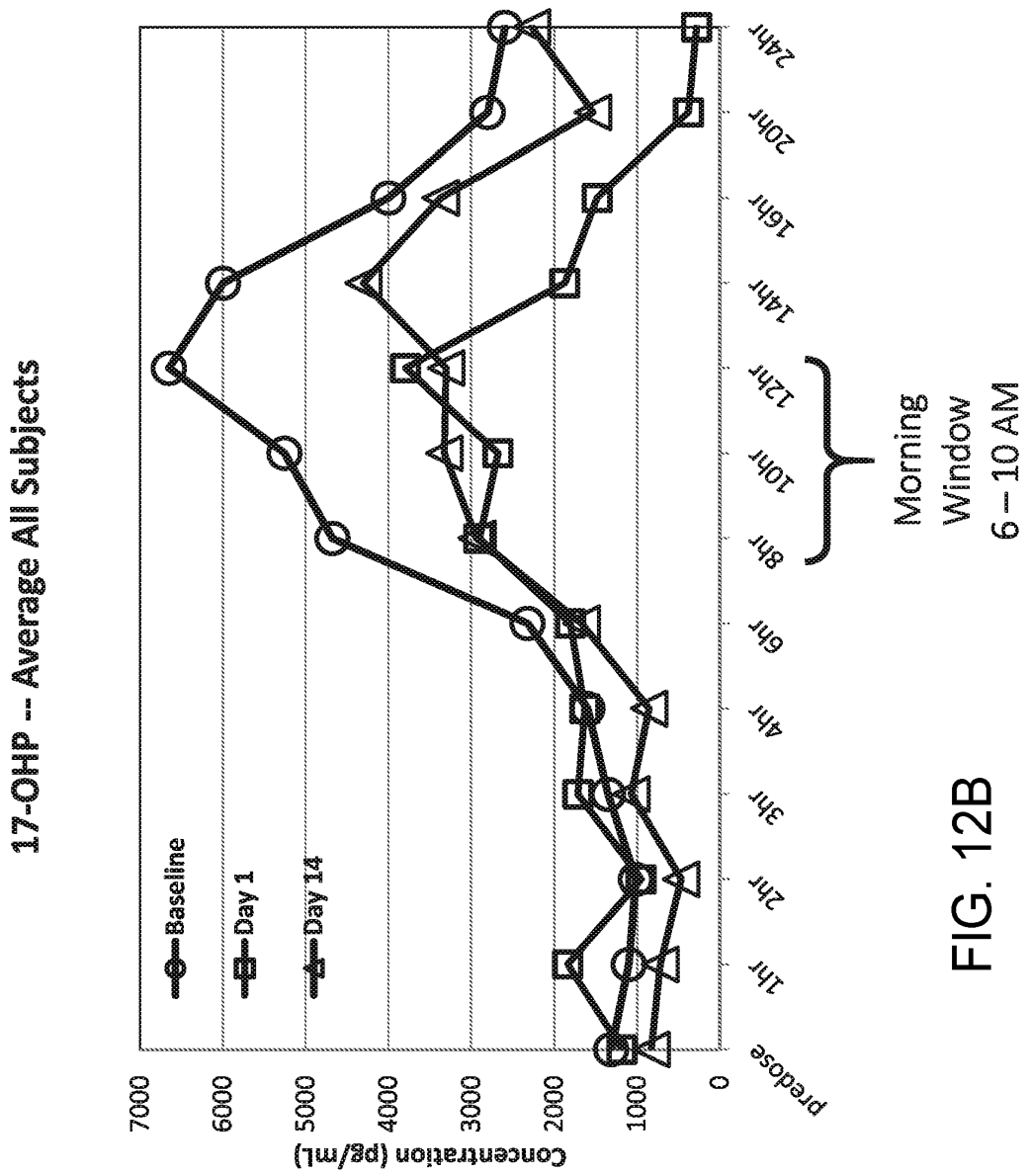

17-OHP -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 12B

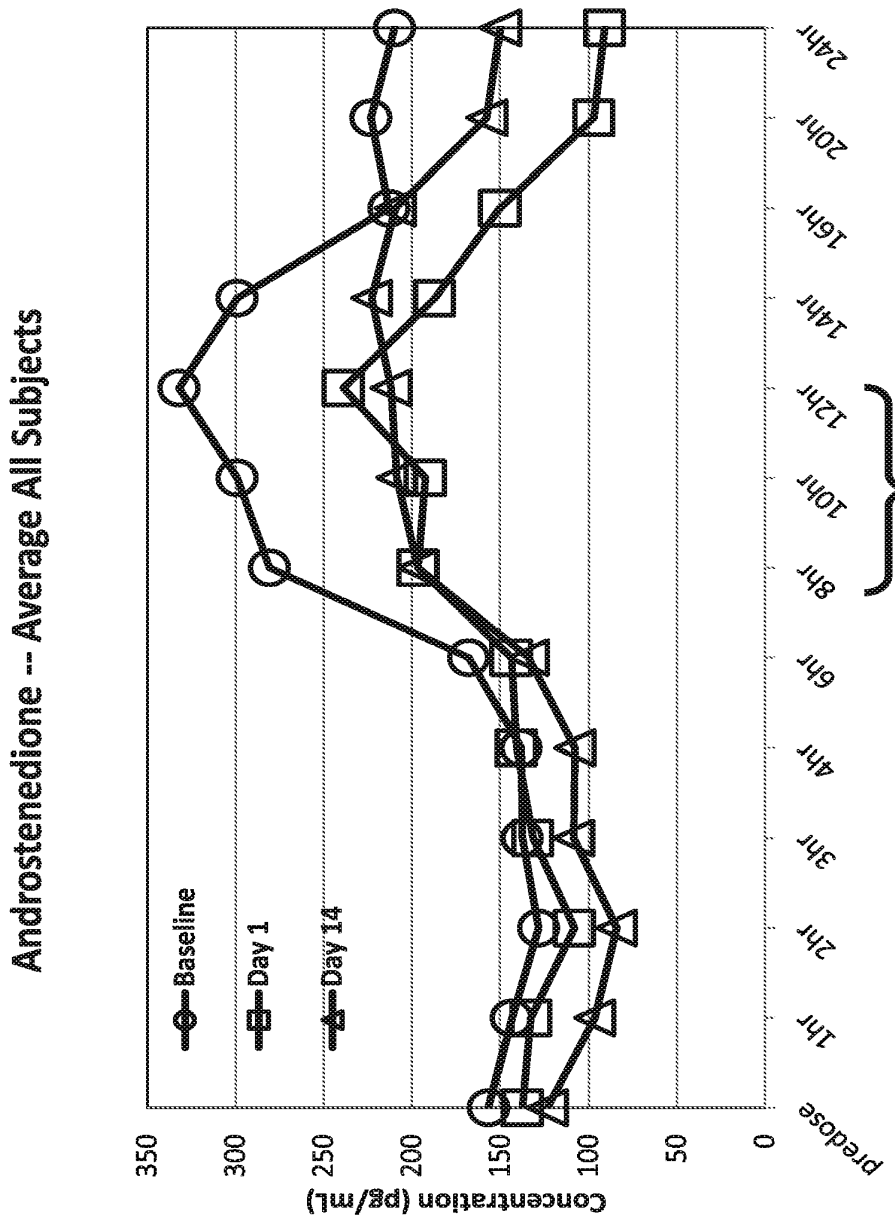

Androstenedione -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
350
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 13A

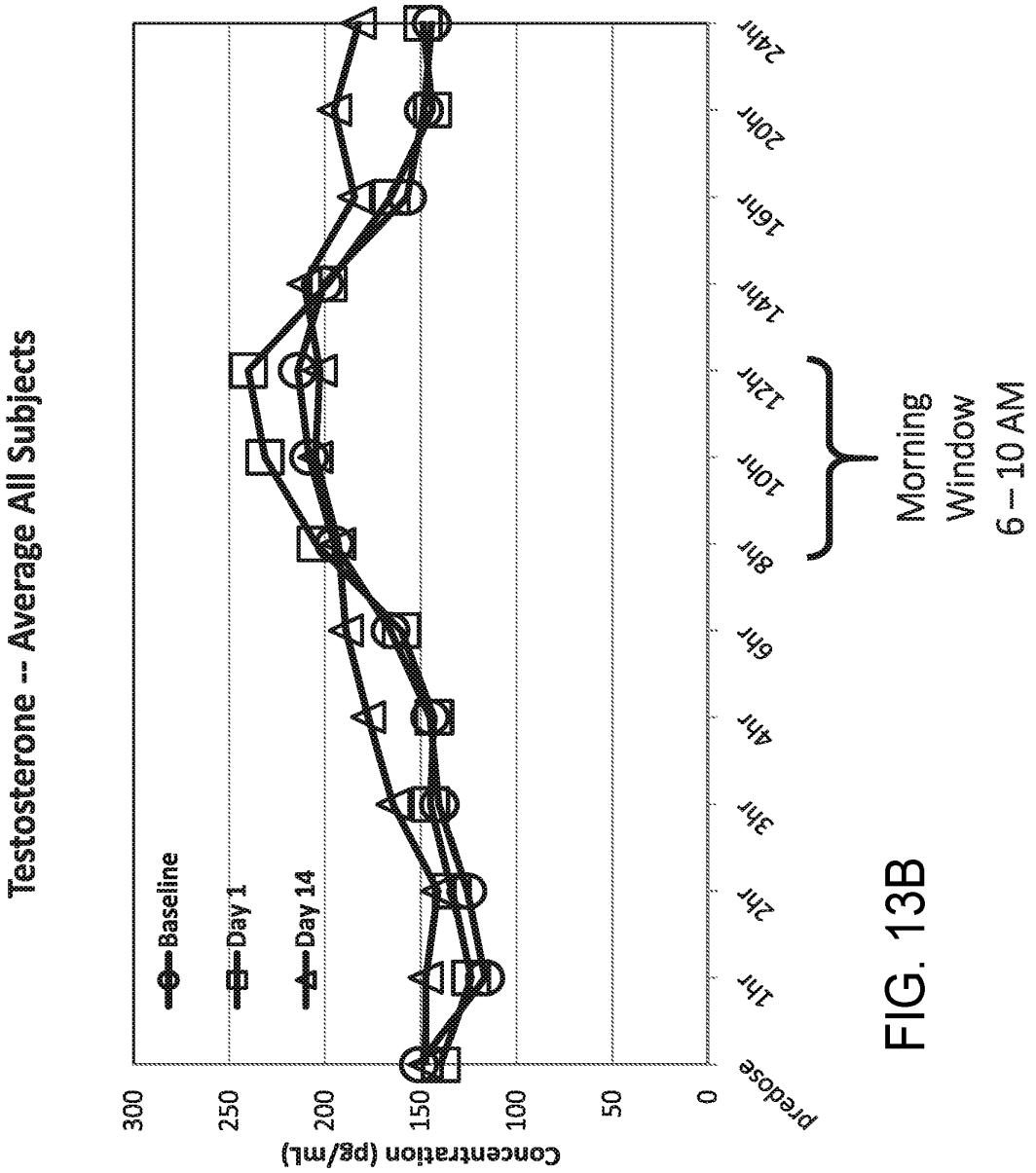

Testosterone -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 13B

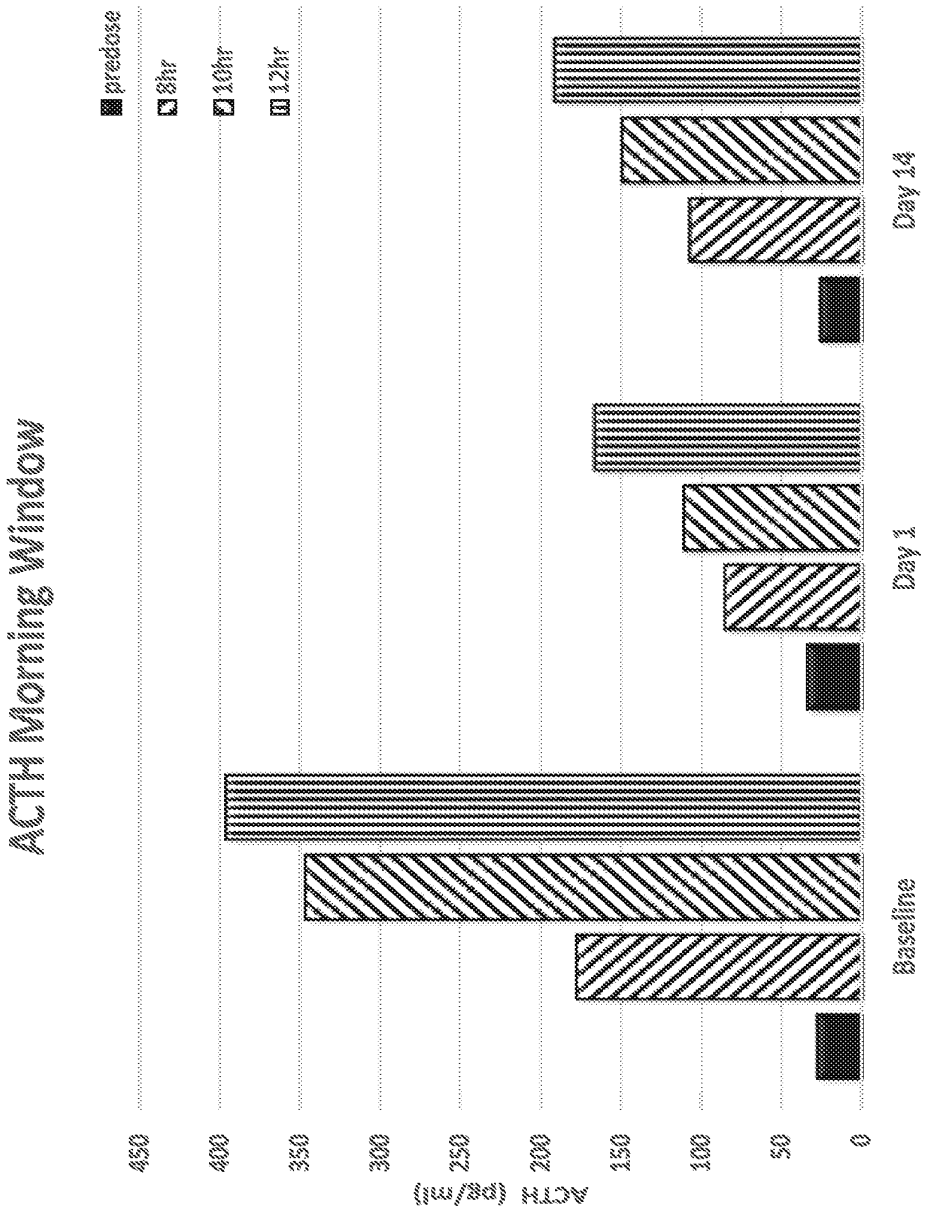

ACTH Morning Window
predose
8hr
10hr
12hr
ACTH (pg/ml)
450
400
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 14A

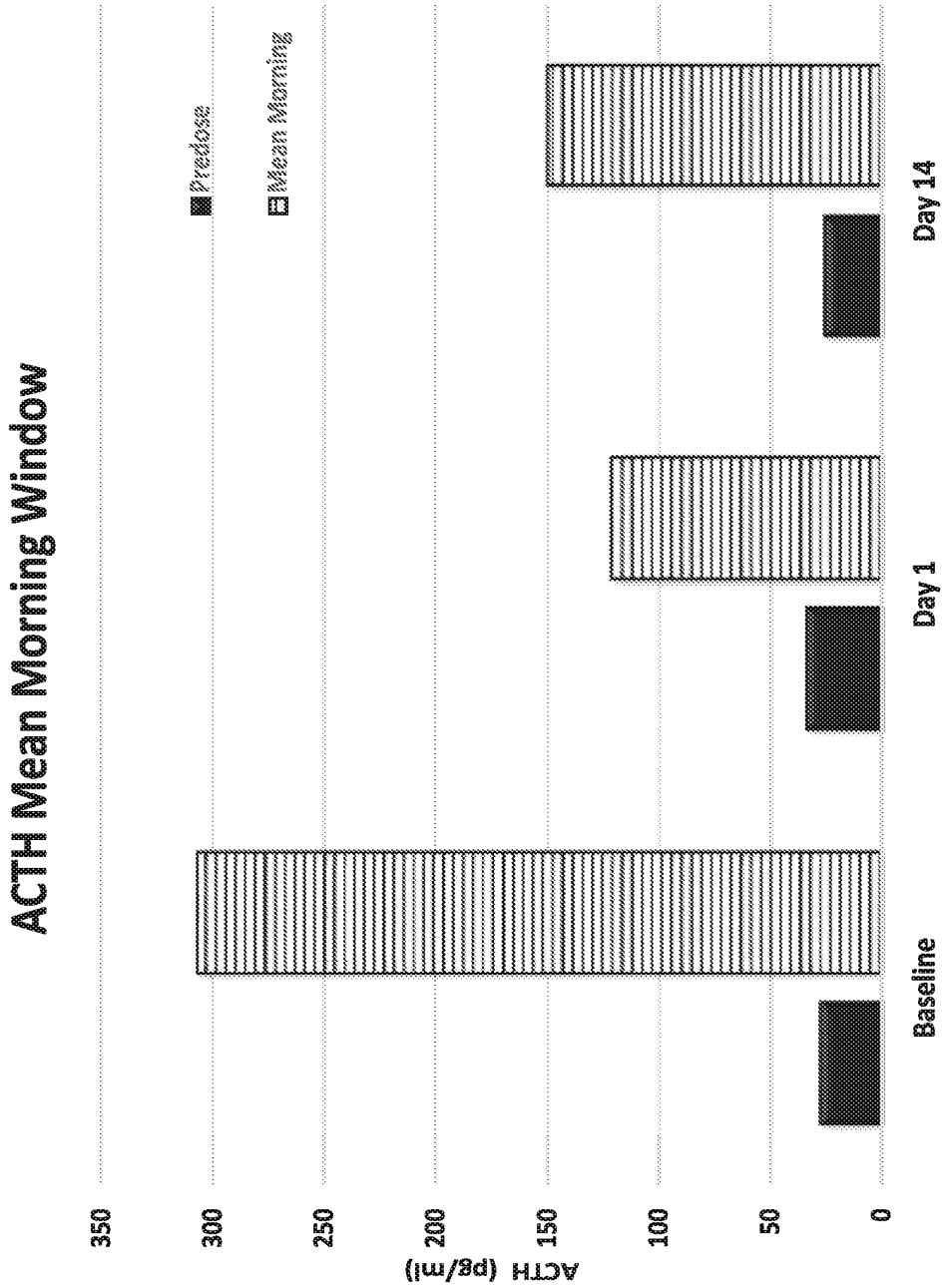

ACTH Mean Morning Window
Predose
Mean Morning
ACTH (pg/ml)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 14B

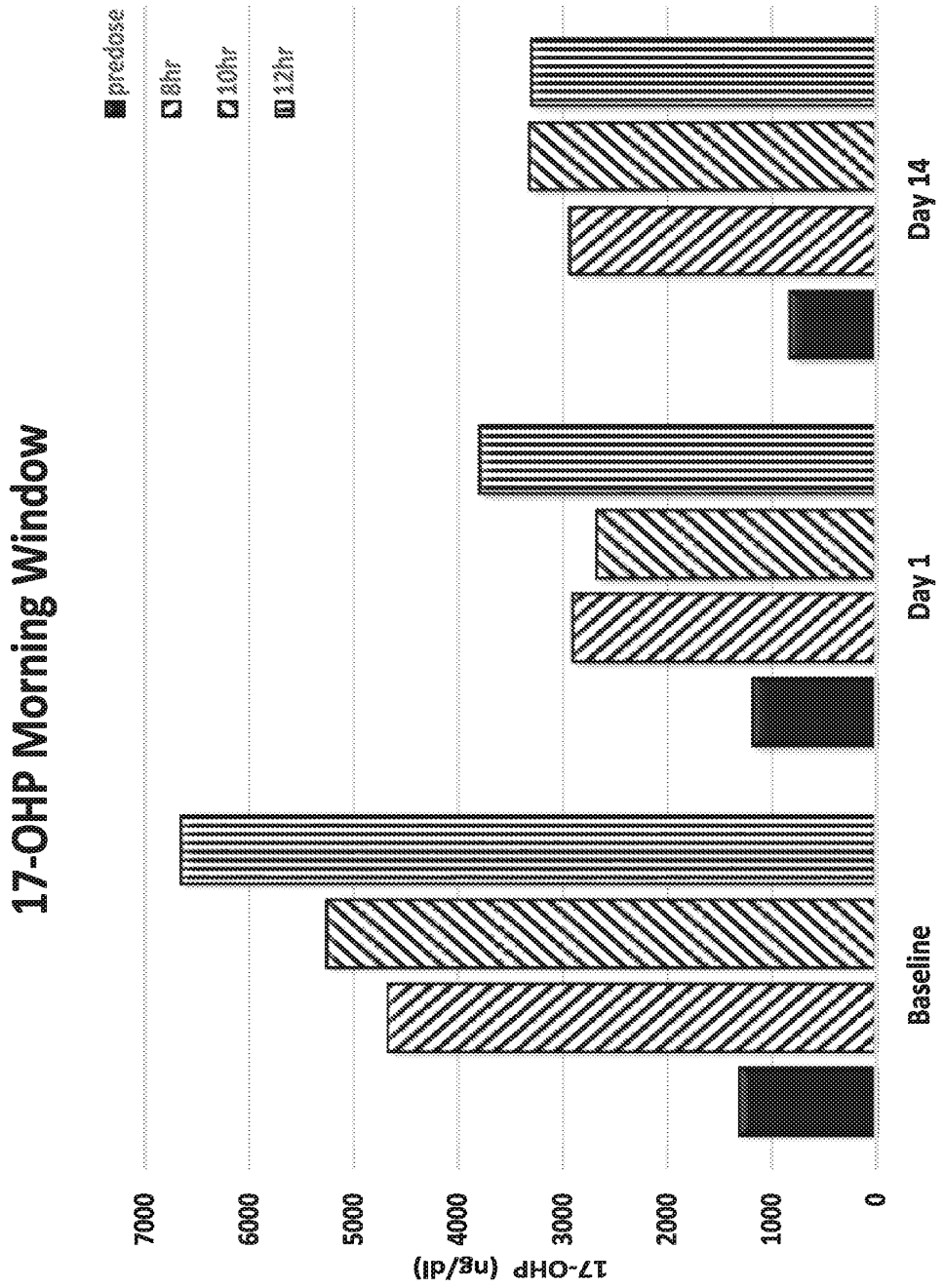

17-OHP Morning Window
predose
2hr
10hr
12hr
17-OHP (ng/dl)
7000
6000
5000
4000
3000
2000
1000
0
Baseline
Day 1
Day 14

FIG. 15A

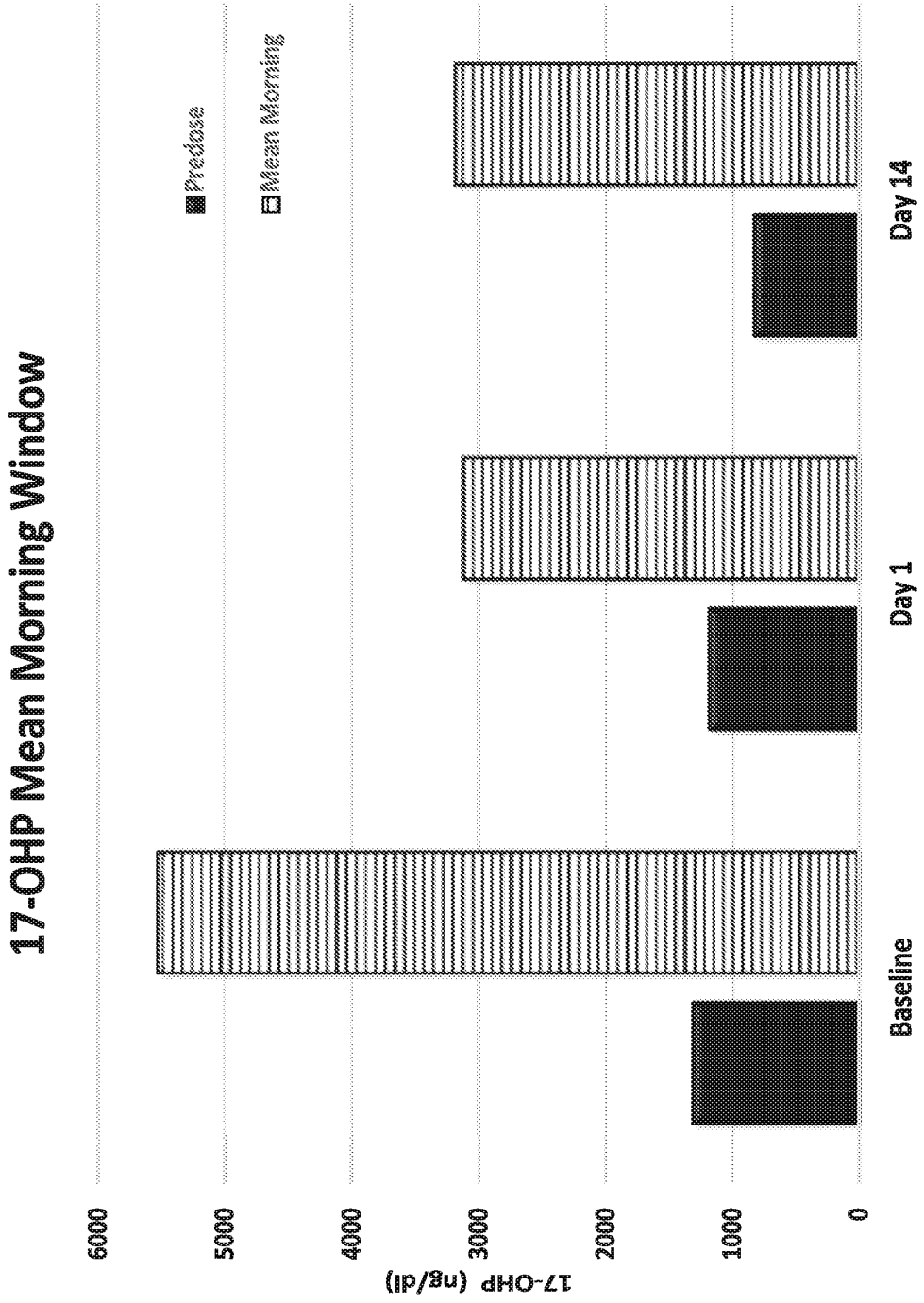

17-OHP Mean Morning Window
Predose
Mean Morning
17-OHP (ng/dl)
6000
5000
4000
3000
2000
1000
0
Baseline
Day 1
Day 14

FIG. 15B

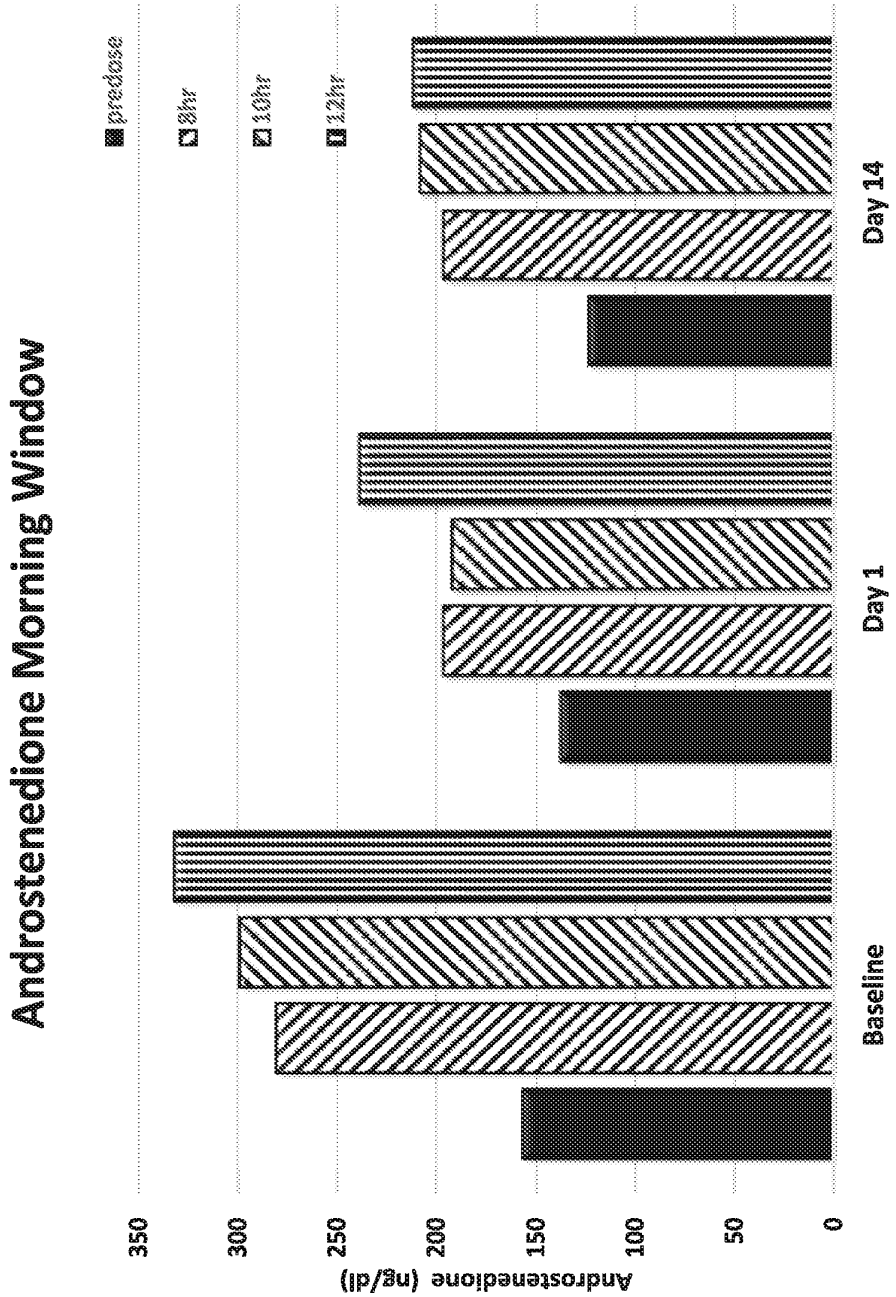

Androstenedione Morning Window
predose
8hr
10hr
12hr
Androstenedione (ng/dl)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 16A

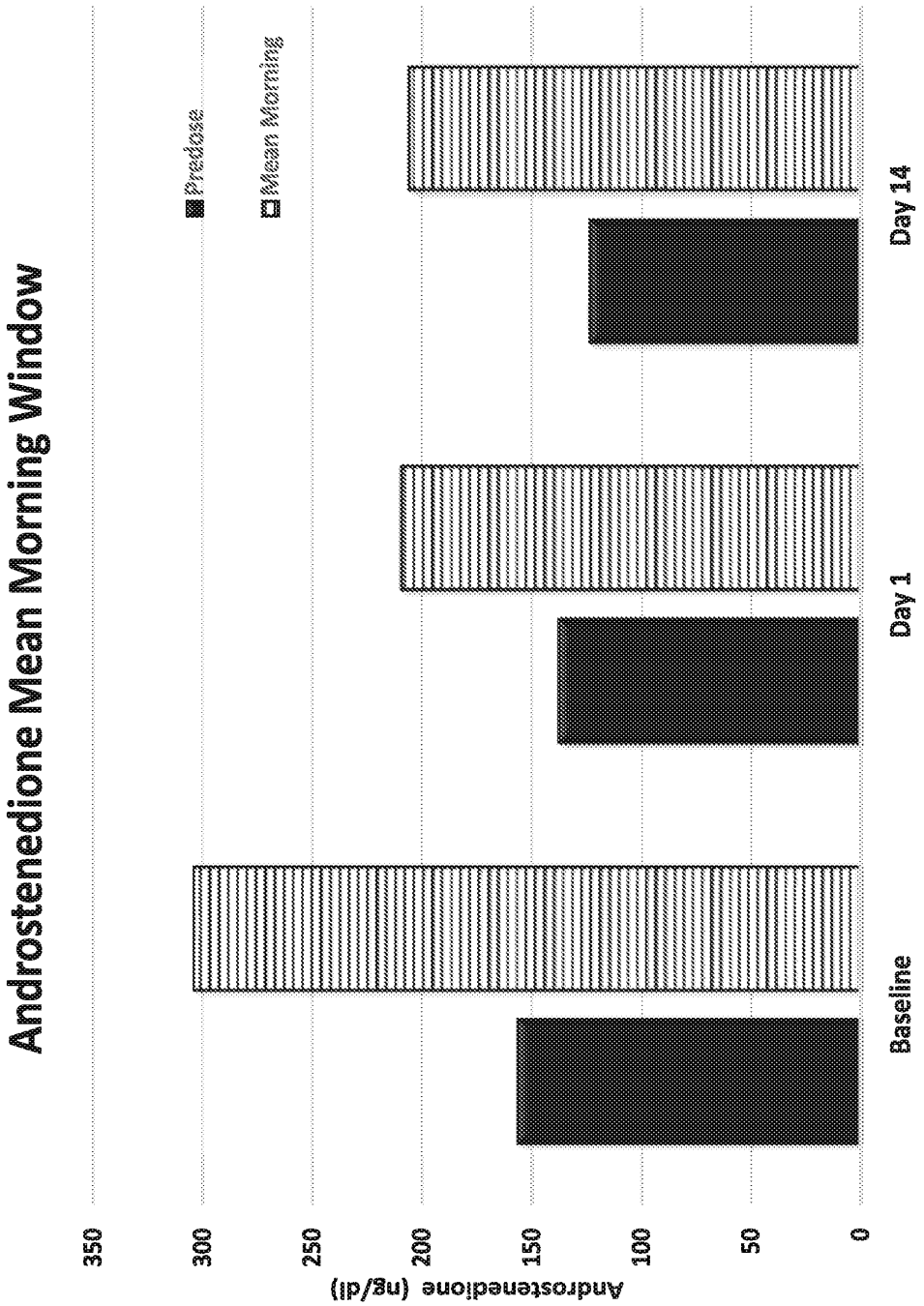

Androstenedione Mean Morning Window
Prednisone
Mean Morning
Androstenedione (ng/dl)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 16B

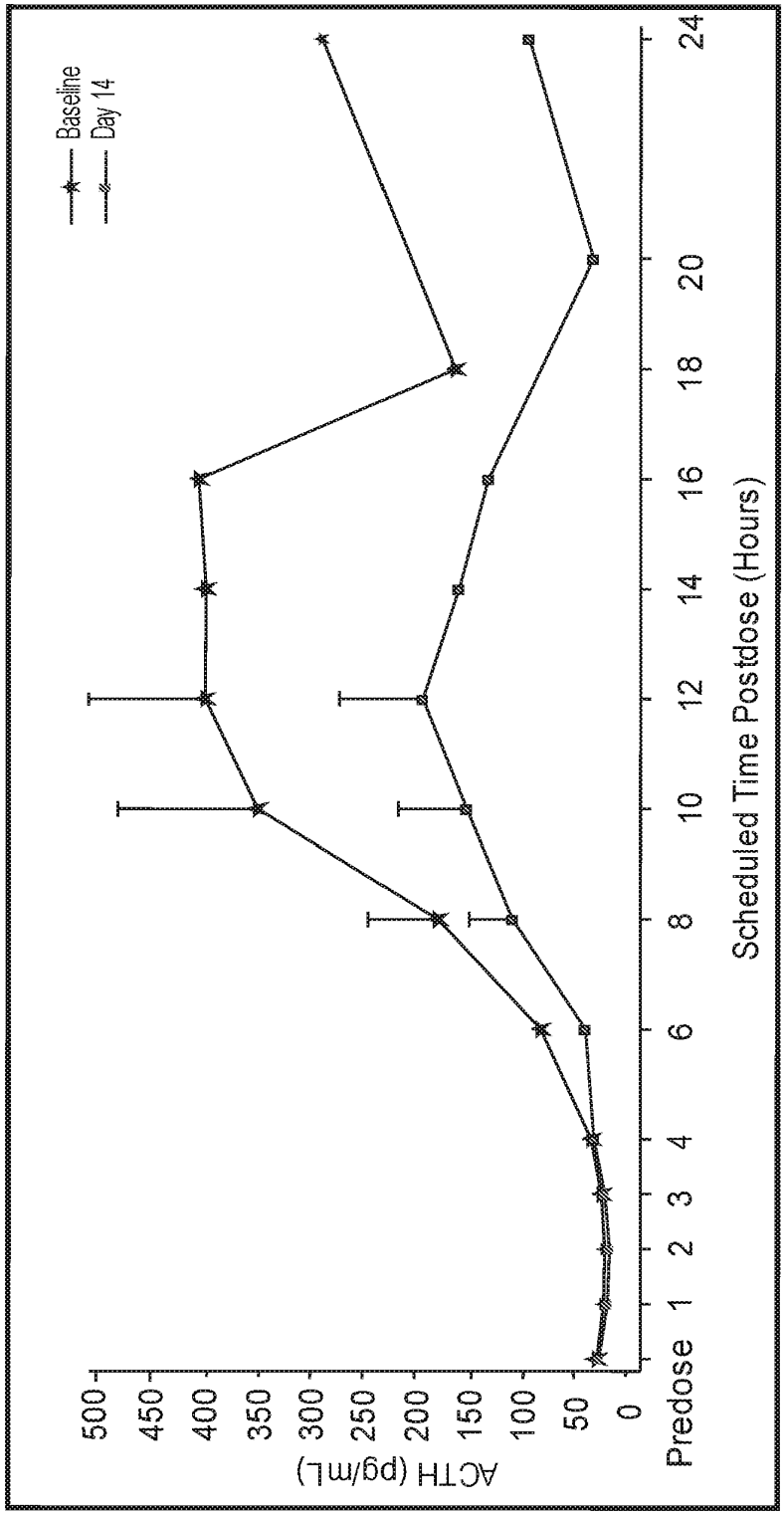

Baseline
Day 14
ACTH (pg/mL)
500
450
400
350
300
250
200
150
100
50
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 17A

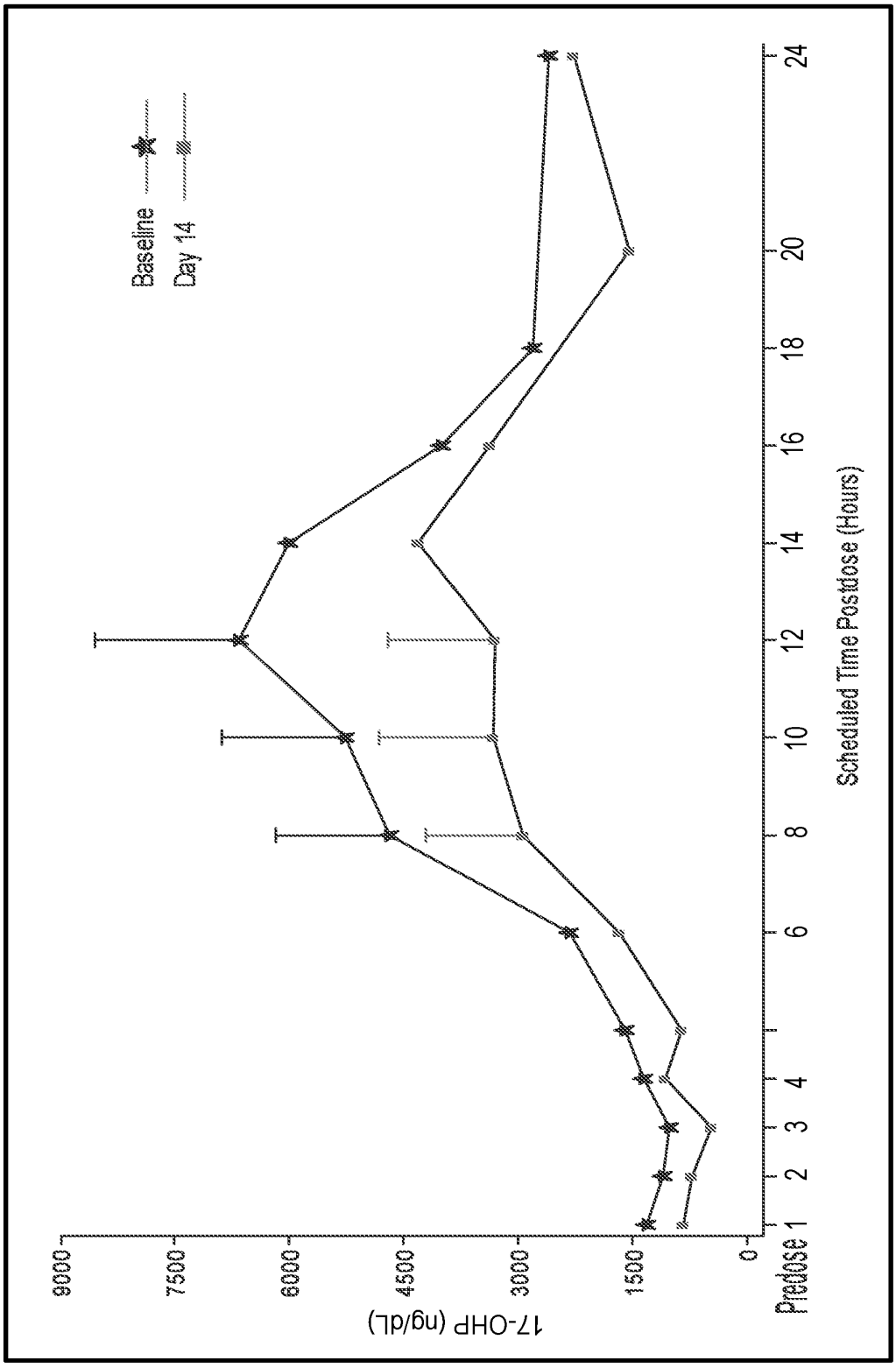

Baseline
Day 14
17-OHP (ng/dL)
9000
7500
6000
4500
3000
1500
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 17B

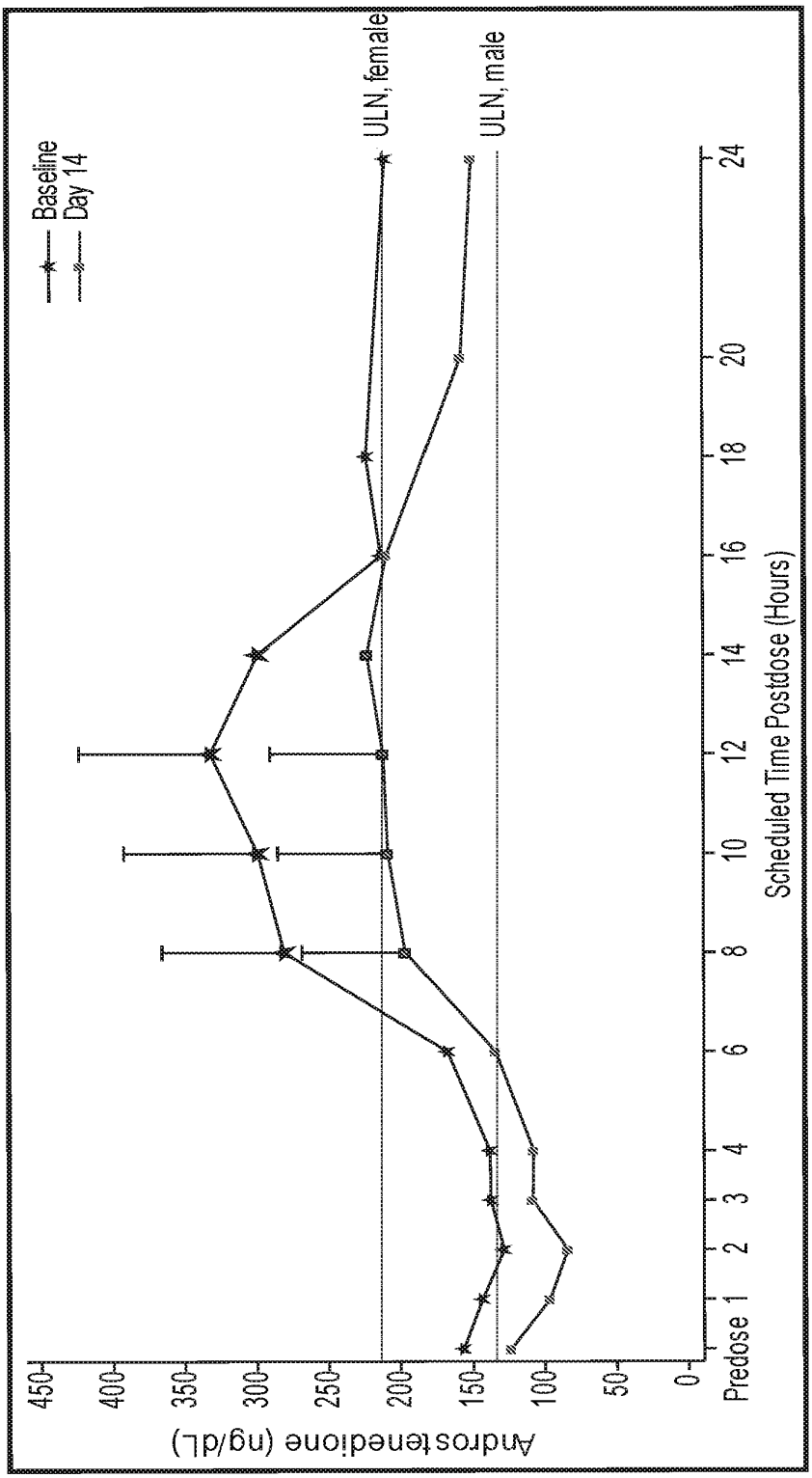

Androstenedione (ng/dL)
450
400
350
300
250
200
150
100
50
0
Predose 1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)
ULN, female
ULN, male
Baseline
Day 14

FIG. 17C

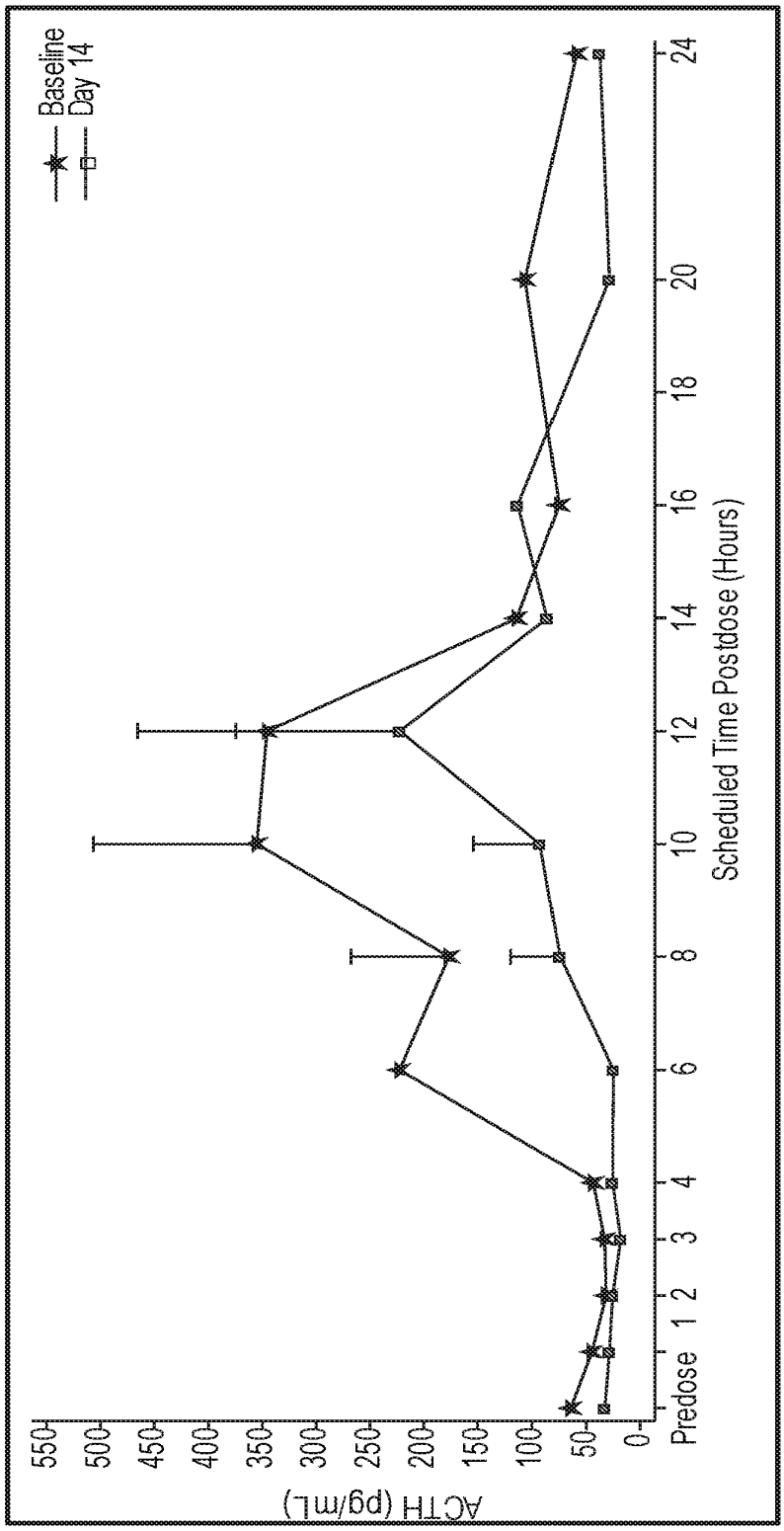

Baseline
Day 14
ACTH (pg/mL)
550
500
450
400
350
300
250
200
150
100
50
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 18A

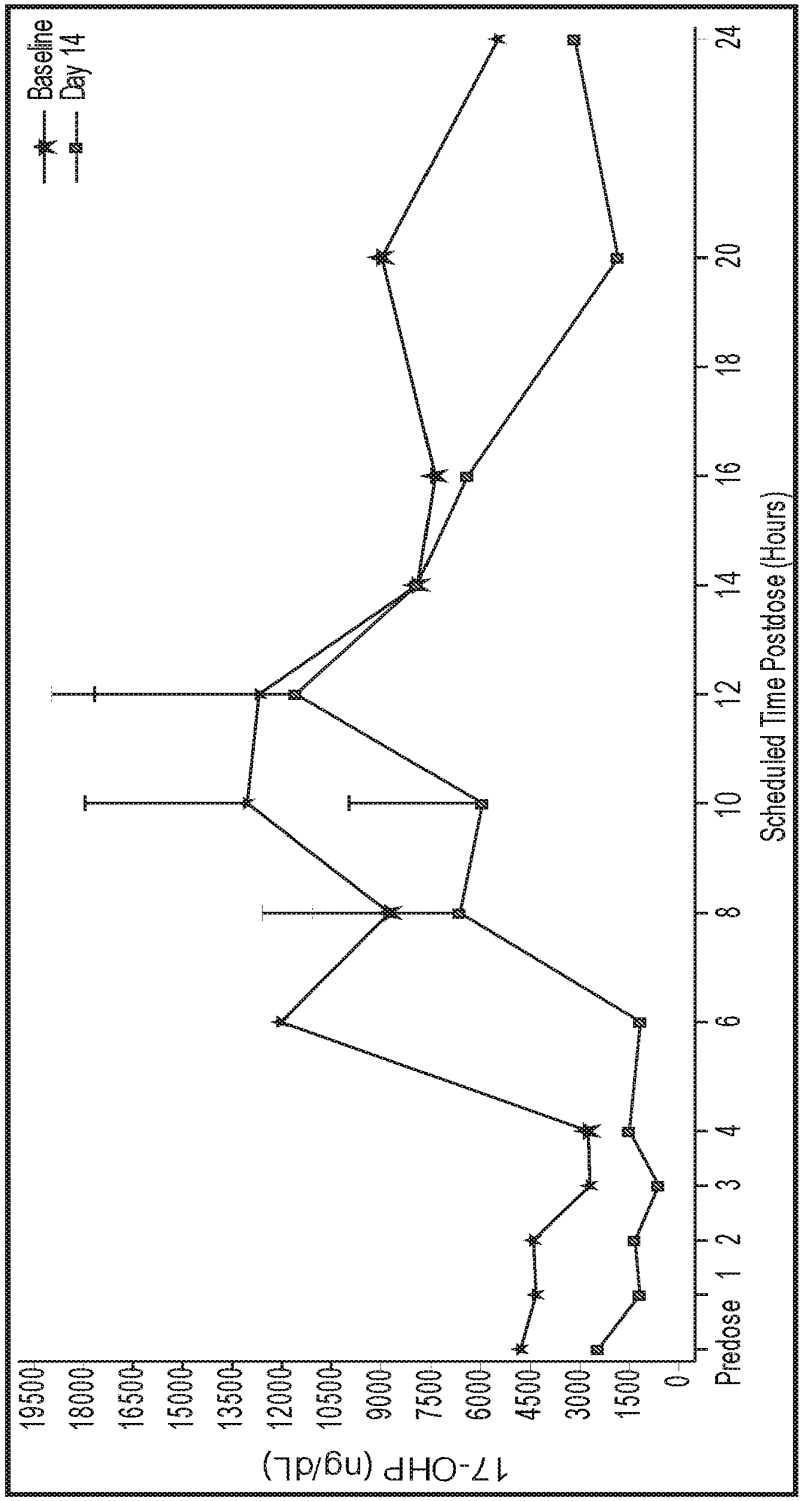

Baseline
Day 14
17-OHP (ng/dL)
19500
18000
16500
15000
13500
12000
10500
9000
7500
6000
4500
3000
1500
0
Predose 1 2 3 4 6 8 10 12 14 16 18 20 24
Scheduled Time Postdose (Hours)

FIG. 18B

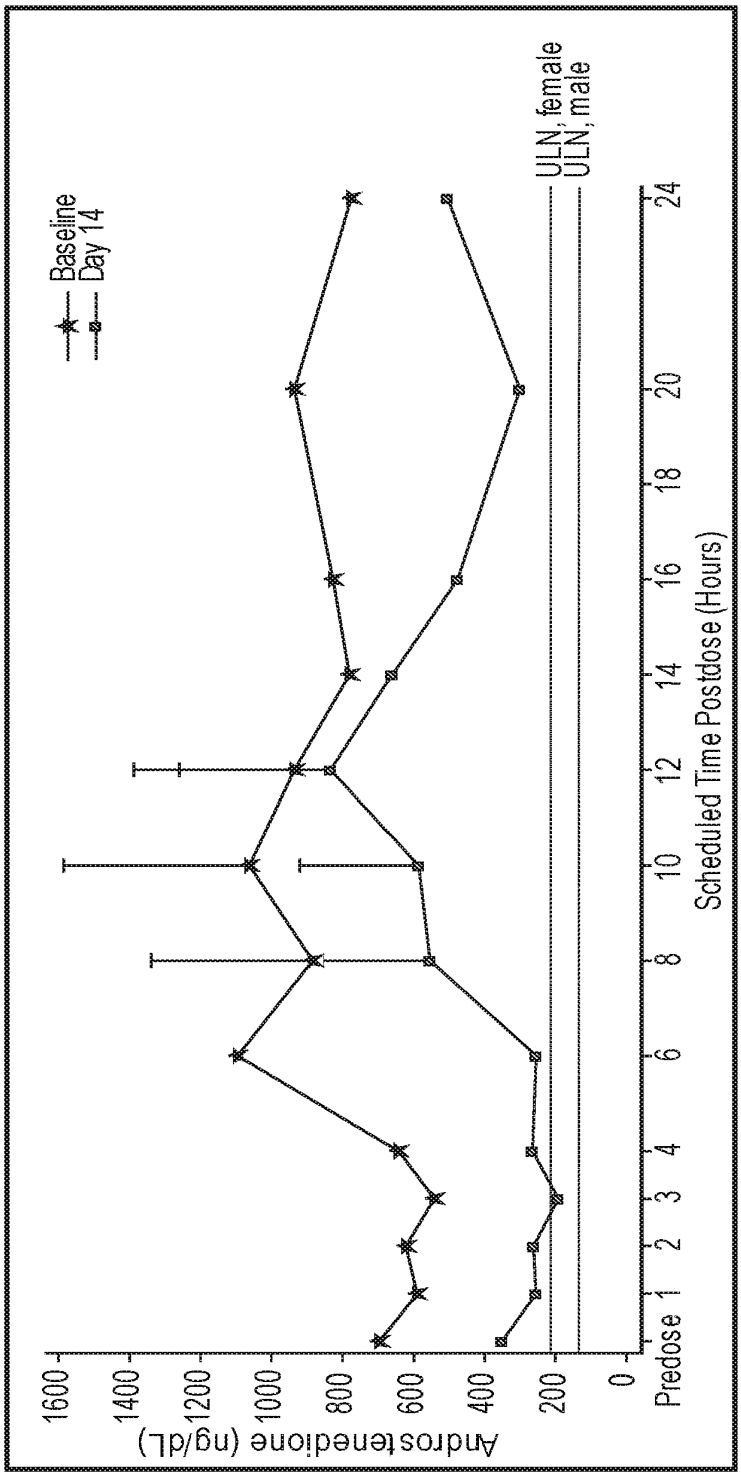

Androstenedione (ng/dL)
1600
1400
1200
1000
800
600
400
200
0
Predose 1 2 3 4 6 8 10 12 14 16 18 20 24
Scheduled Time Postdose (Hours)
Baseline
Day 14
ULN, female
ULN, male

FIG. 18C

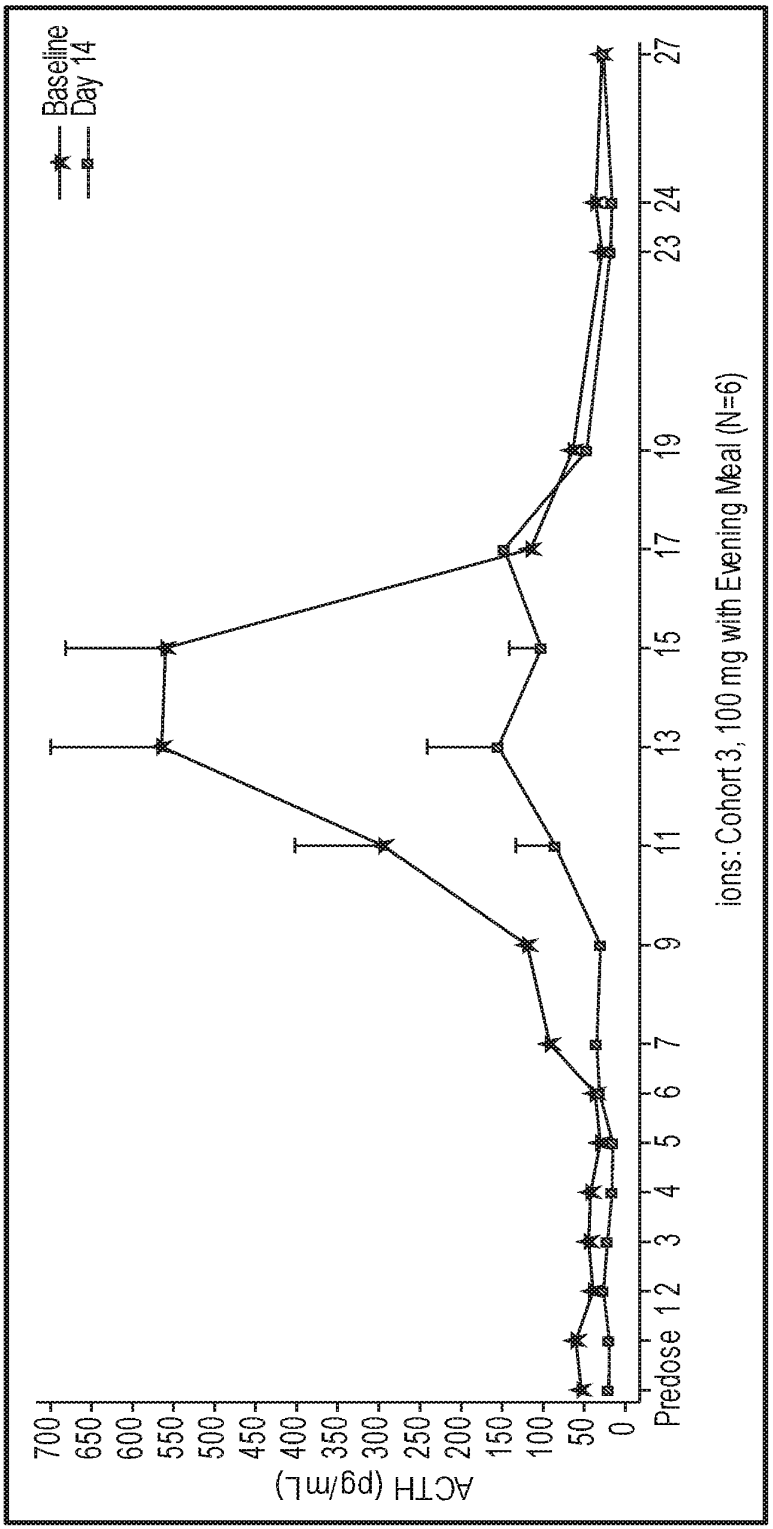

Baseline
Day 14
ACTH (pg/mL)
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
ions: Cohort 3, 100 mg with Evening Meal (N=6)

FIG. 19A

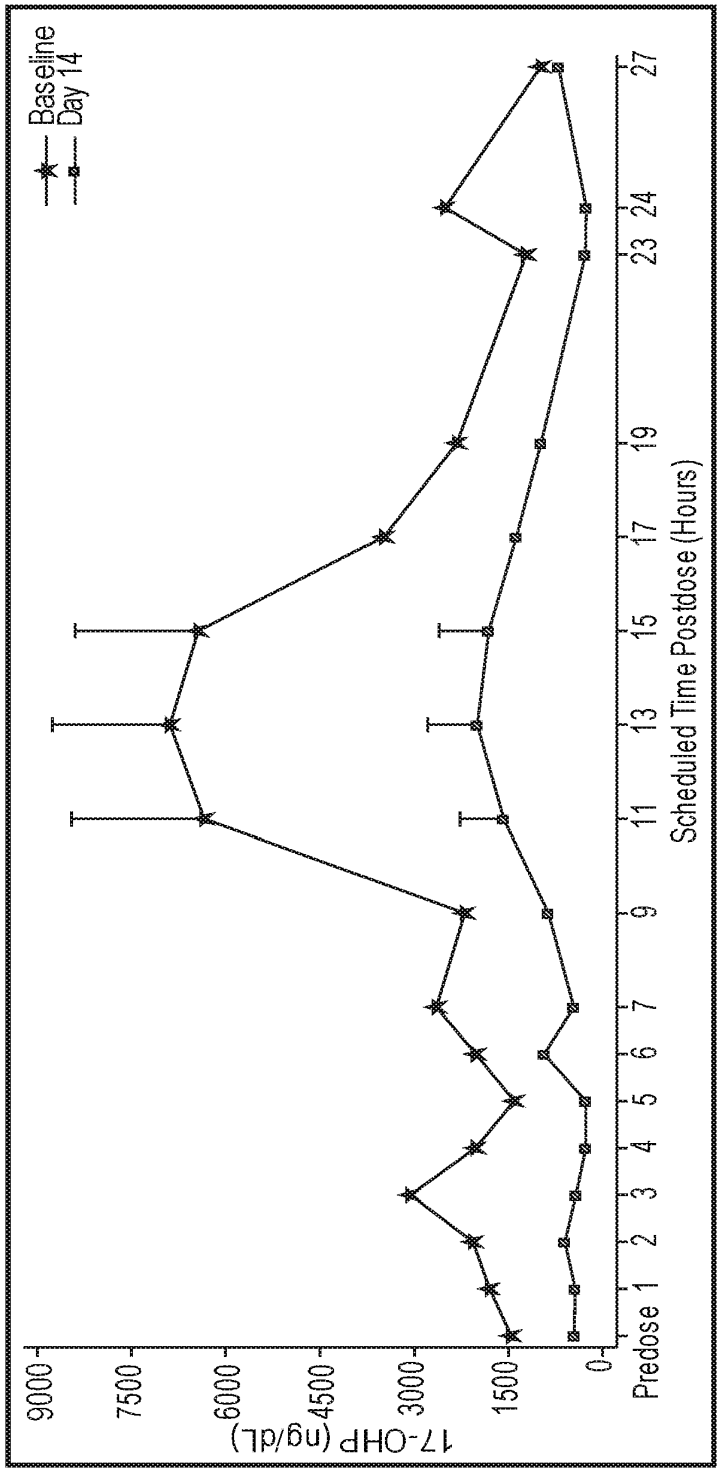

Baseline
Day 14
17-OHP (ng/dL)
9000
7500
6000
4500
3000
1500
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
Scheduled Time Postdose (Hours)

FIG. 19B

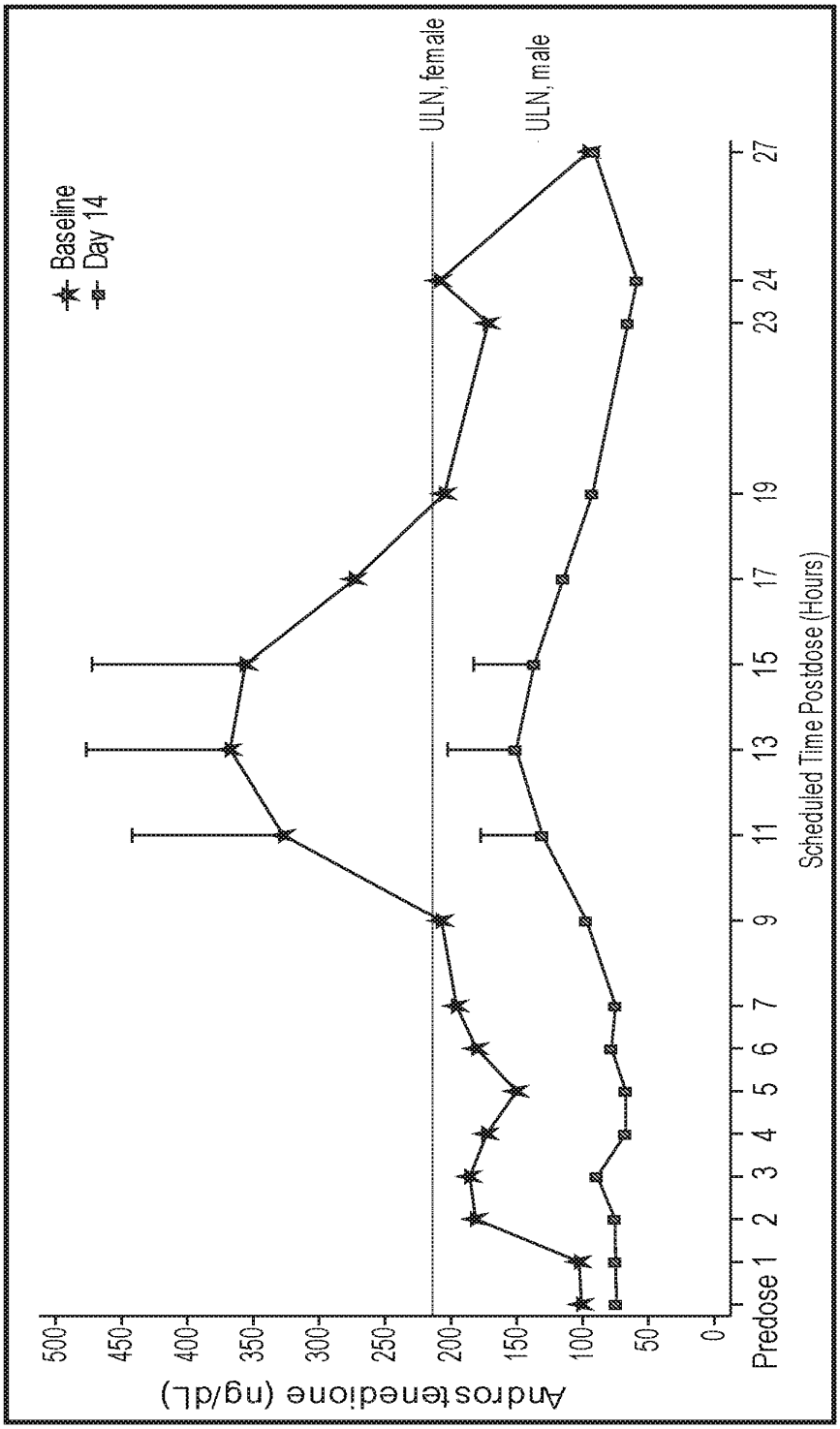

Baseline
Day 14
ULN, female
ULN, male
Androstenedione (ng/dL)
500
450
400
350
300
250
200
150
100
50
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
Scheduled Time Postdose (Hours)

FIG. 19C

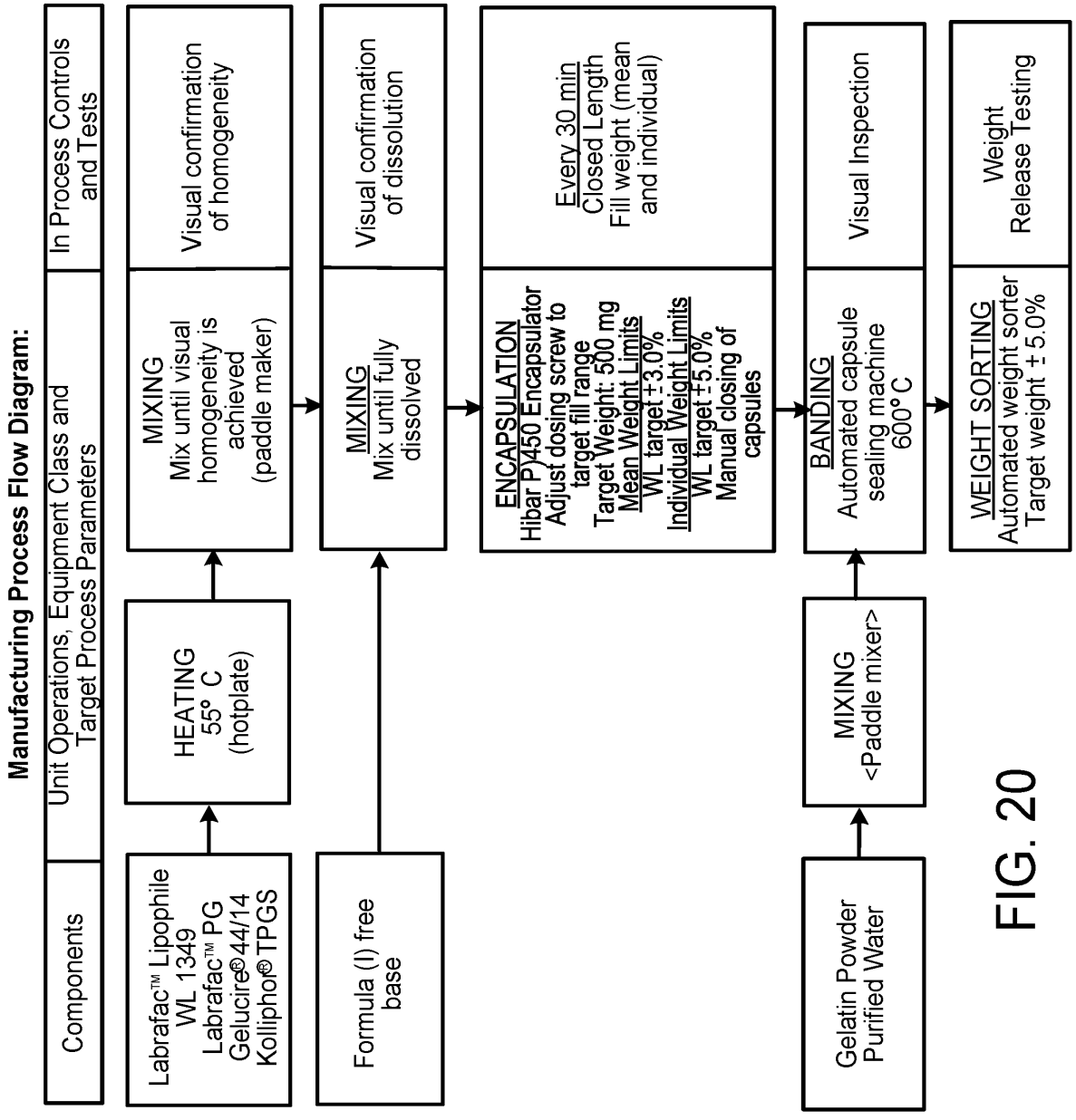
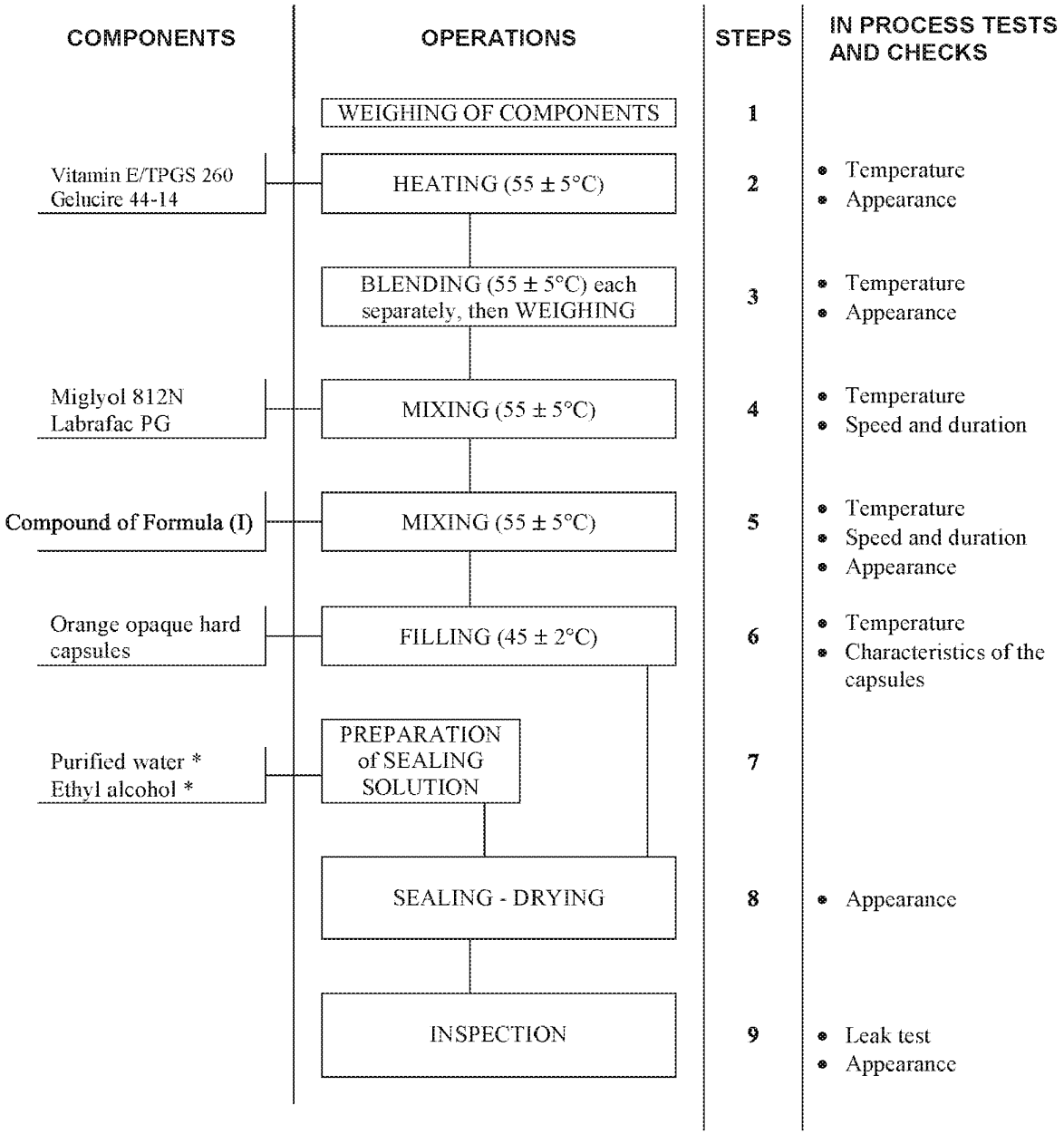

Manufacturing Process Flow Diagram:
Components
Unit Operations, Equipment Class and Target Process Parameters
In Process Controls and Tests
Labrafac™ Lipophile WL 1349
Labrafac™ PG
Gelucire® 44/14
Kolliphor® TPGS
HEATING 55° C (hotplate)
MIXING Mix until visual homogeneity is achieved (paddle maker)
Visual confirmation of homogeneity
Formula (I) free base
MIXING Mix until fully dissolved
Visual confirmation of dissolution
ENCAPSULATION Hibar P/450 Encapsulator Adjust dosing screw to target fill range Target Weight: 500 mg Mean Weight Limits WL target ±3.0% Individual Weight Limits WL target ±5.0% Manual closing of capsules
Every 30 min Closed Length Fill weight (mean and individual)
Gelatin Powder Purified Water
MIXING <Paddle mixer>
BANDING Automated capsule sealing machine 600° C
Visual Inspection
WEIGHT SORTING Automated weight sorter Target weight ± 5.0%
Weight Release Testing

FIG. 20



* Can be contained in hydro-alcoholic solution ready for manufacturing use

FIG. 21

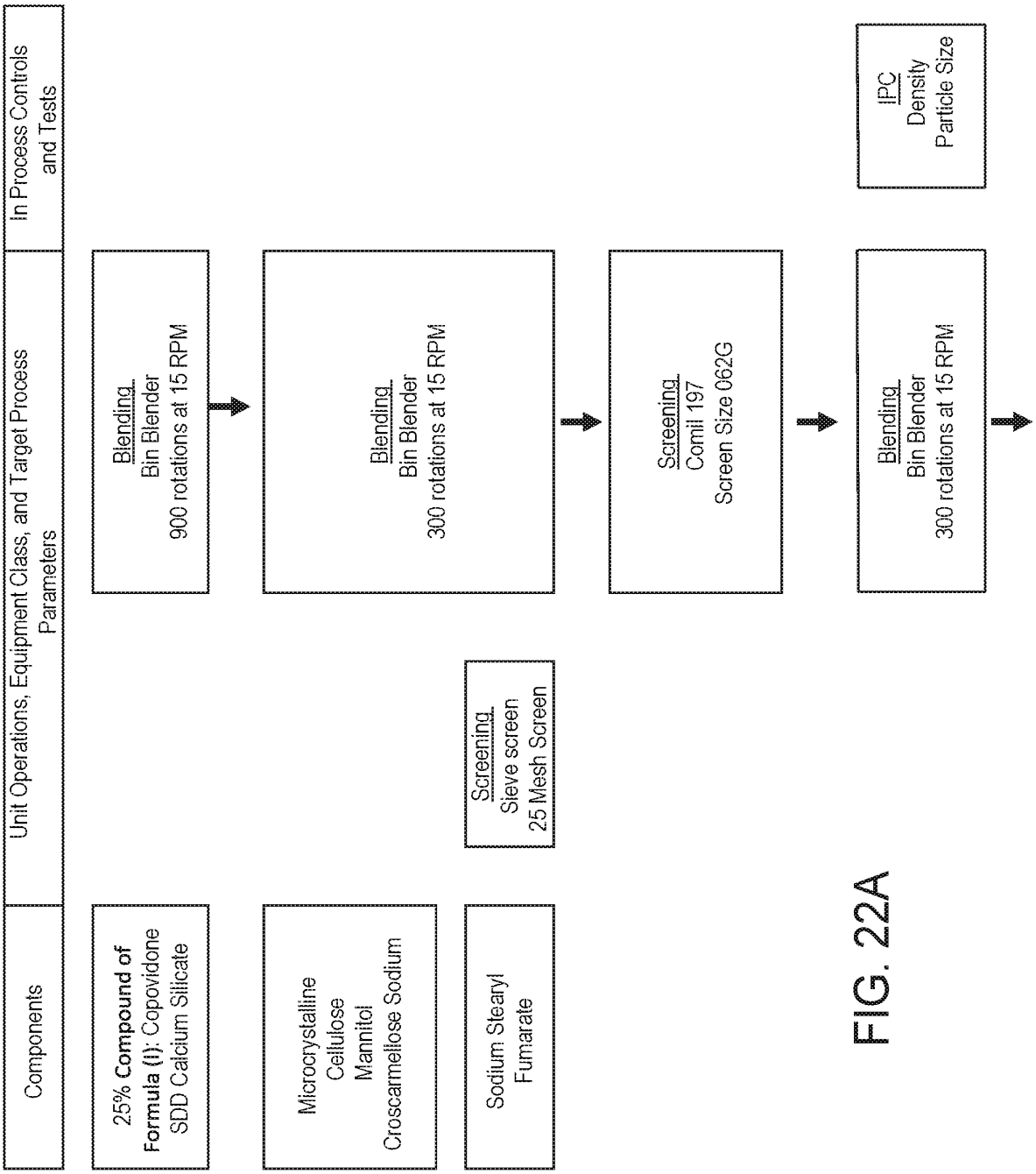

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
25% Compound of Formula (I): Copovidone SDD Calcium Silicate
Blending
Bin Blender
900 rotations at 15 RPM
Microcrystalline Cellulose Mannitol Croscarmellose Sodium
Blending
Bin Blender
300 rotations at 15 RPM
Sodium Stearyl Fumarate
Screening
Sieve screen
25 Mesh Screen
Screening
Comil 197
Screen Size 062G
Blending
Bin Blender
300 rotations at 15 RPM
IPC
Density
Particle Size

FIG. 22A

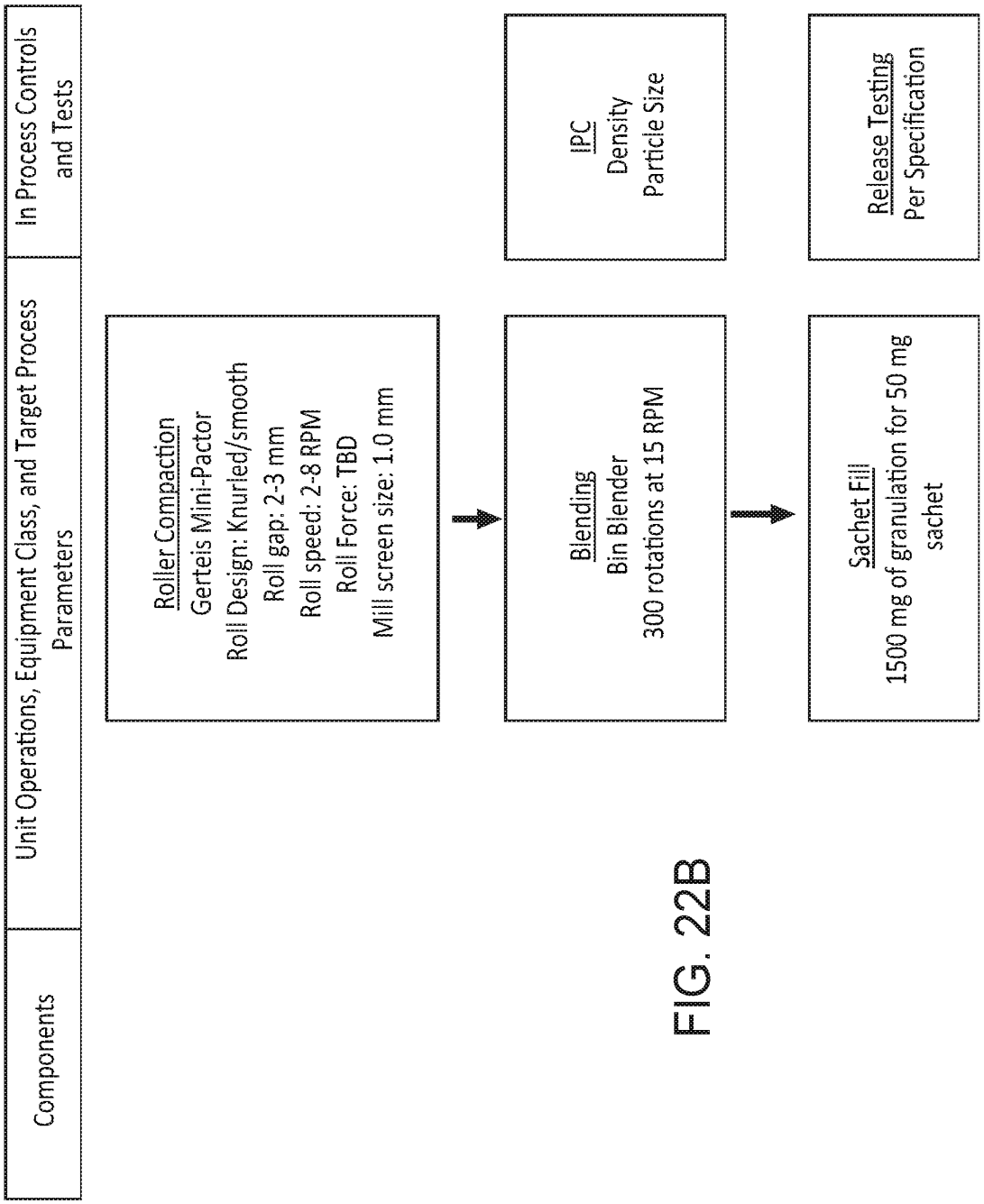

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
Roller Compaction
Gerteis Mini-Pactor
Roll Design: Knurled/smooth
Roll gap: 2-3 mm
Roll speed: 2-8 RPM
Roll Force: TBD
Mill screen size: 1.0 mm
Blending
Bin Blender
300 rotations at 15 RPM
IPC
Density
Particle Size
Sachet Fill
1500 mg of granulation for 50 mg sachet
Release Testing
Per Specification

FIG. 22B

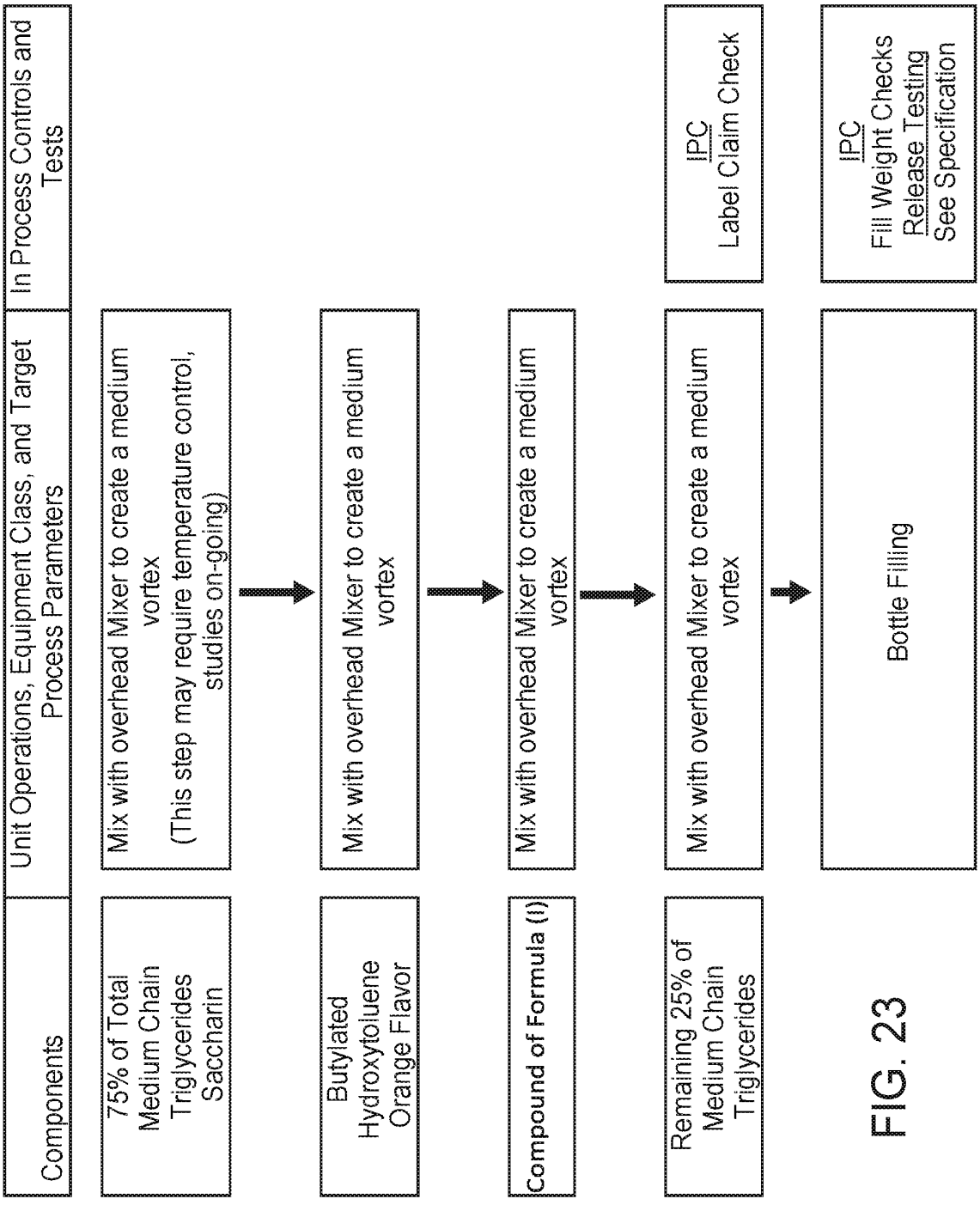

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
75% of Total Medium Chain Triglycerides Saccharin
Mix with overhead Mixer to create a medium vortex (This step may require temperature control, studies on-going)
Butylated Hydroxytoluene Orange Flavor
Mix with overhead Mixer to create a medium vortex
Compound of Formula (I)
Mix with overhead Mixer to create a medium vortex
Remaining 25% of Medium Chain Triglycerides
Mix with overhead Mixer to create a medium vortex
Bottle Filling
IPC Label Claim Check
IPC Fill Weight Checks Release Testing See Specification

FIG. 23

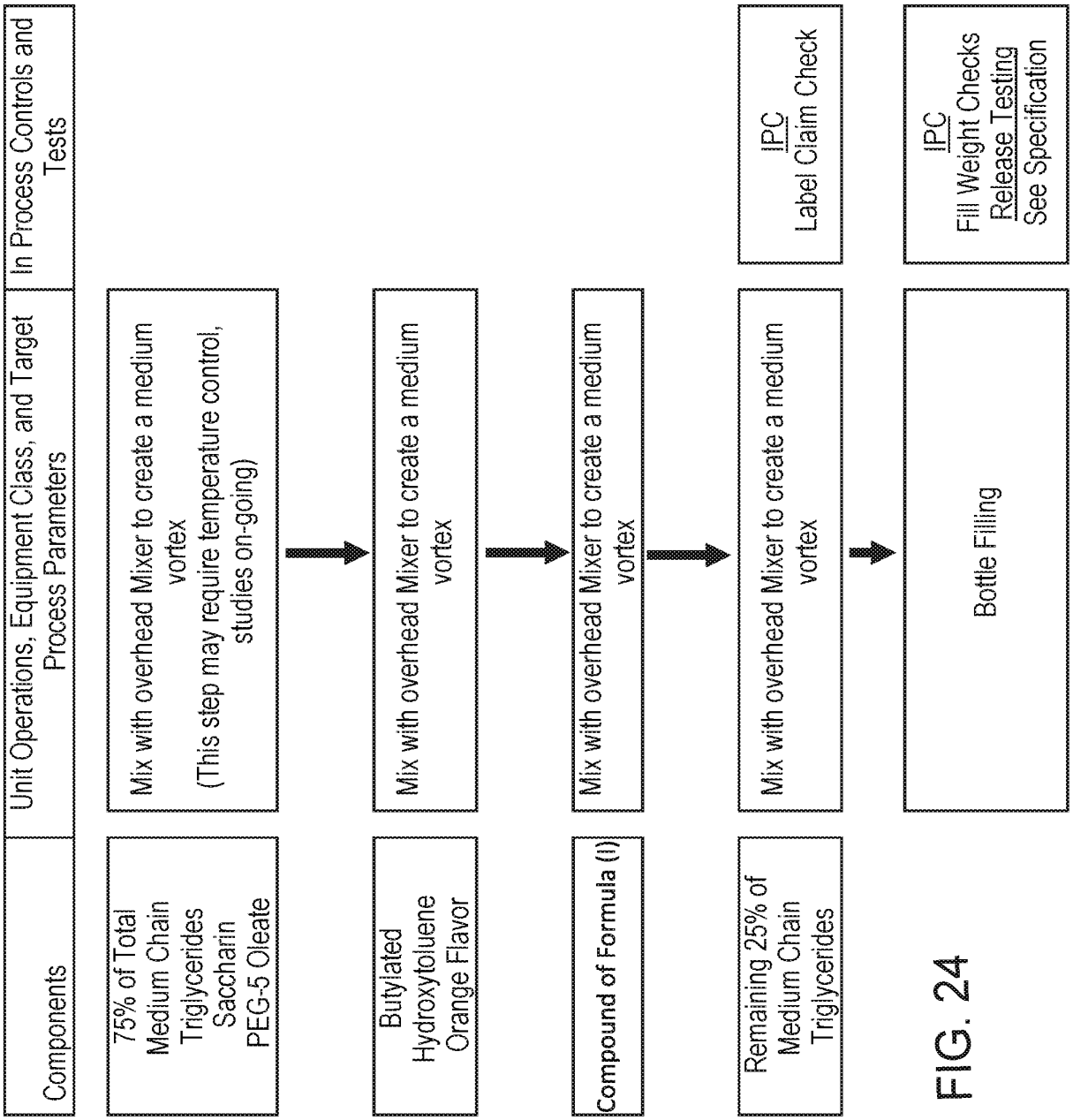

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
75% of Total Medium Chain Triglycerides
Saccharin
PEG-5 Oleate
Mix with overhead Mixer to create a medium vortex
(This step may require temperature control, studies on-going)
Butylated Hydroxytoluene
Orange Flavor
Mix with overhead Mixer to create a medium vortex
Compound of Formula (I)
Mix with overhead Mixer to create a medium vortex
Remaining 25% of Medium Chain Triglycerides
Mix with overhead Mixer to create a medium vortex
IPC
Label Claim Check
Bottle Filling
IPC
Fill Weight Checks
Release Testing
See Specification

FIG. 24

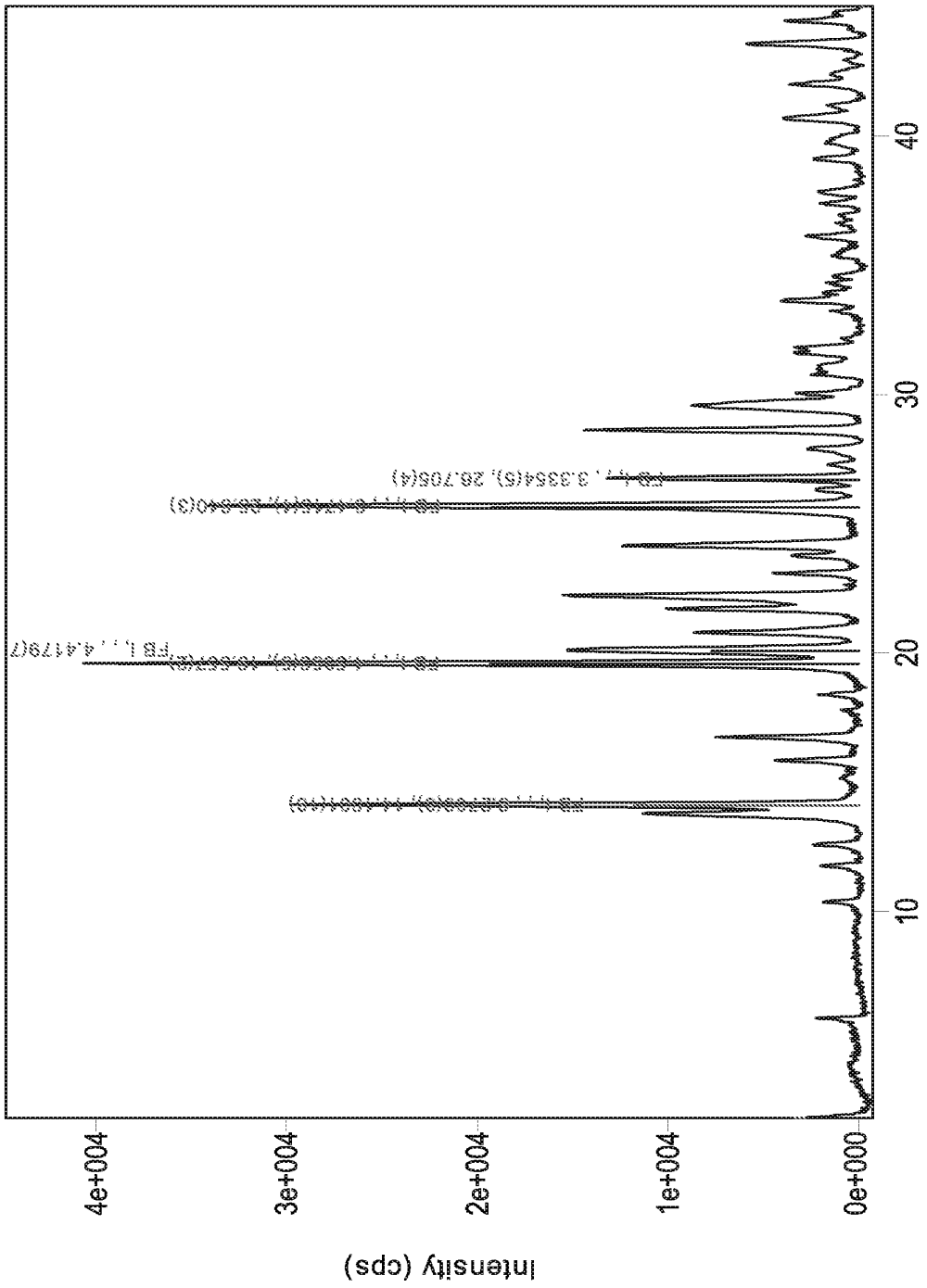

Intensity (cps)
4e+004
3e+004
2e+004
1e+004
0e+000
10
20
30
40
2-theta (deg)

FIG. 25

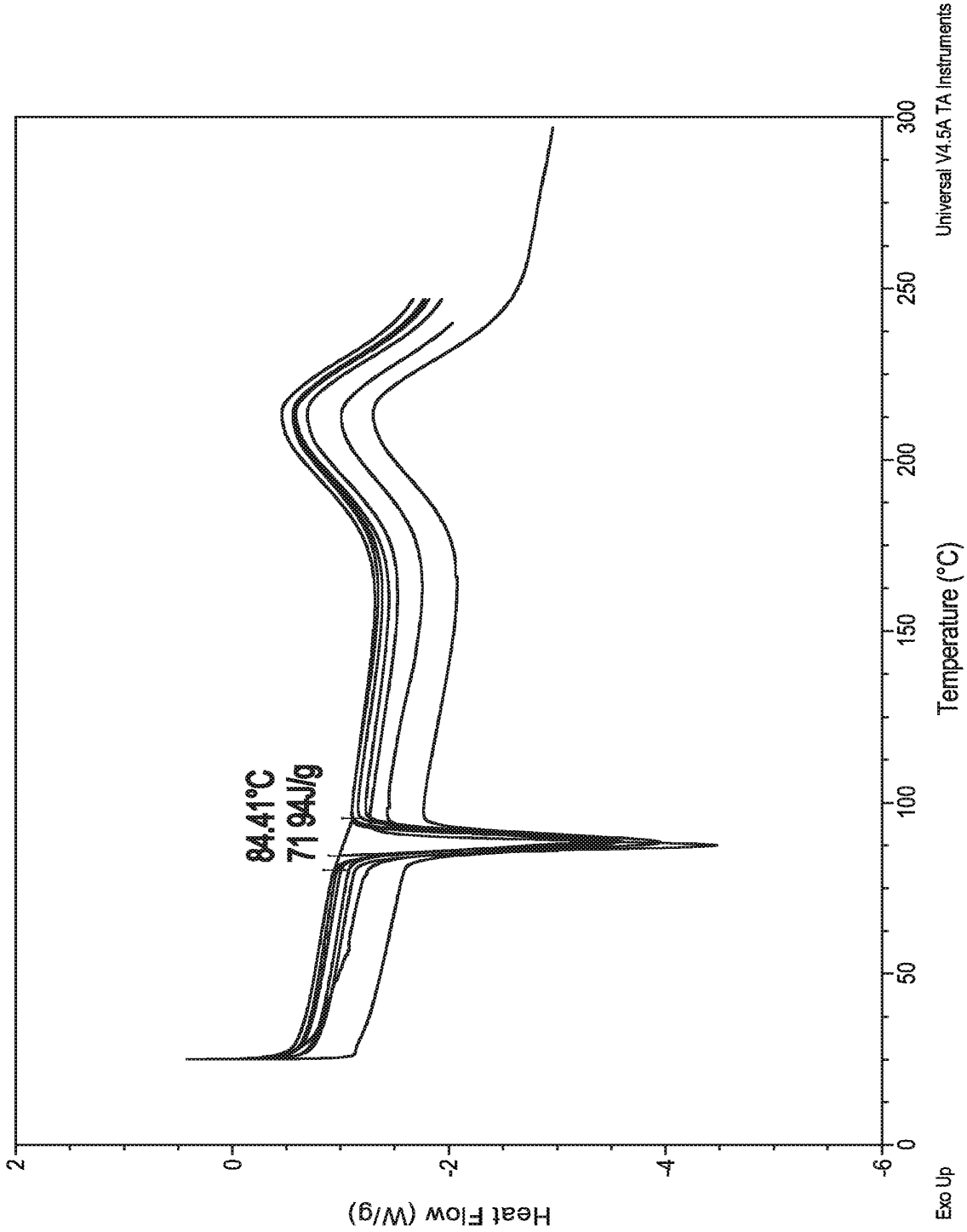

84.41°C
71.94J/g
Heat Flow (W/g)
Exo Up
Temperature (°C)
Universal V4.5A TA Instruments
2
0
-2
-4
-6
0
50
100
150
200
250
300

FIG. 26

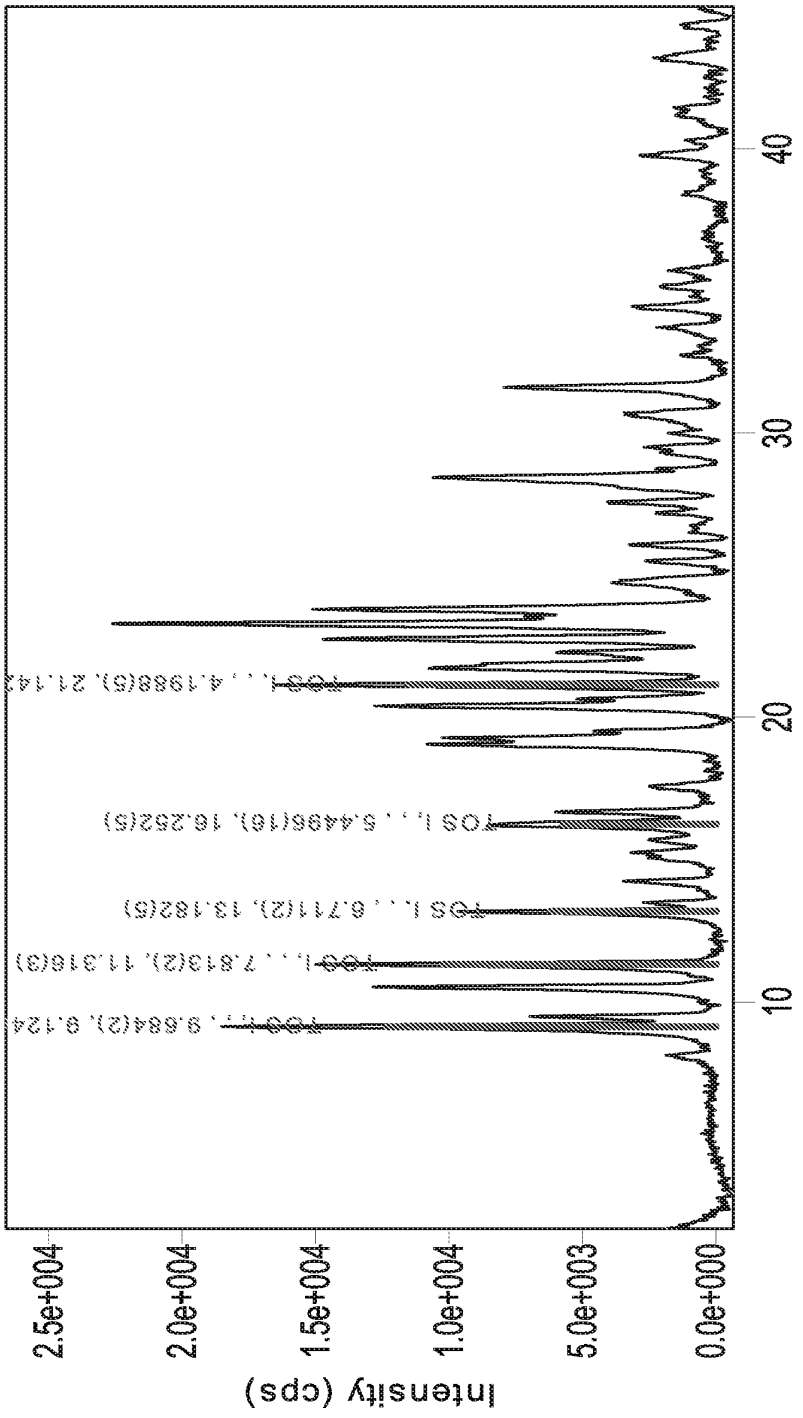

Intensity (cps)
2.5e+004
2.0e+004
1.5e+004
1.0e+004
5.0e+003
0.0e+000
10
20
30
40
2-theta (deg)

FIG. 27

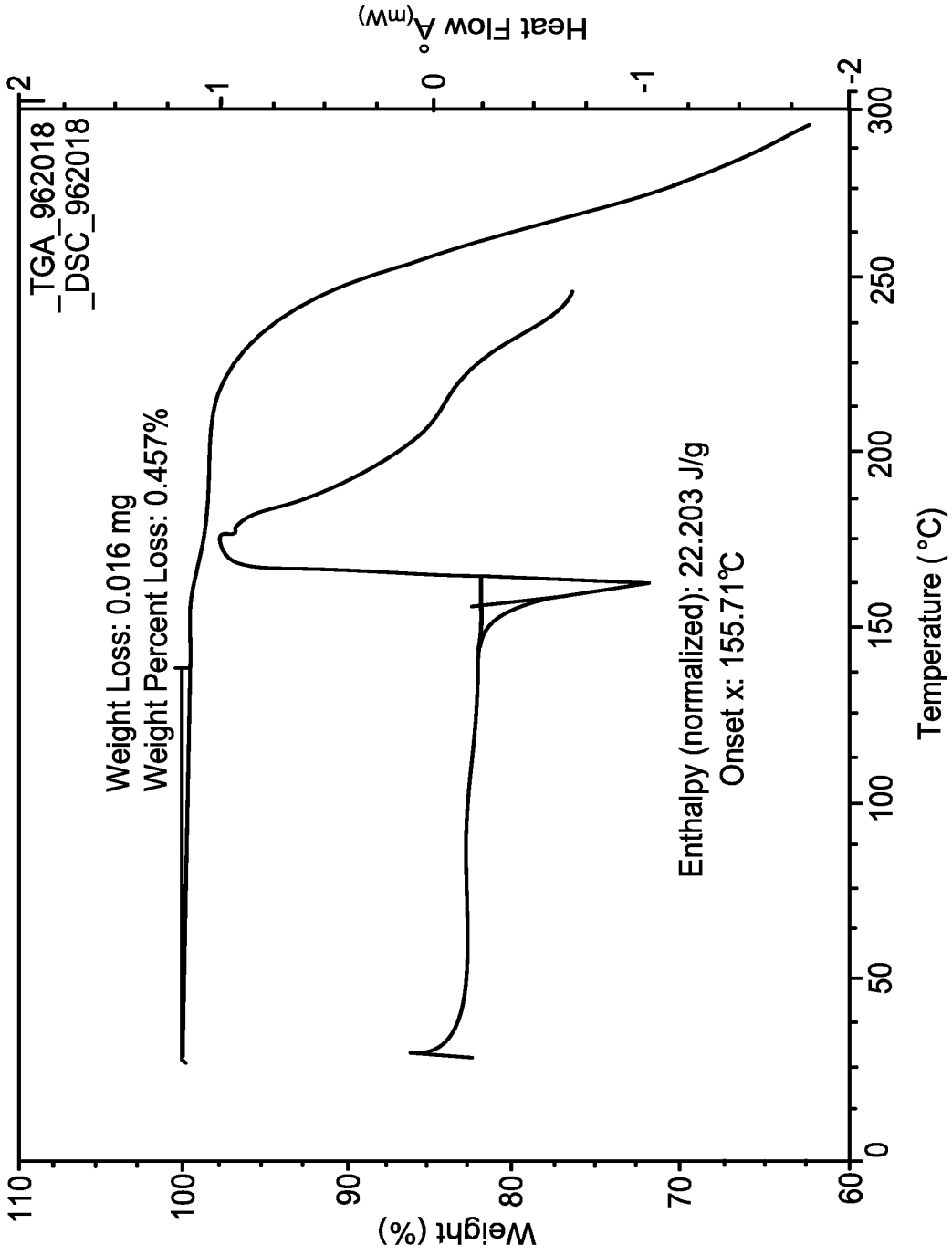

_TGA_962018
_DSC_962018
Weight Loss: 0.016 mg
Weight Percent Loss: 0.457%
Enthalpy (normalized): 22.203 J/g
Onset x: 155.71°C
Weight (%)
Heat Flow A (mW)
Temperature (°C)
110
100
90
80
70
60
2
1
0
-1
-2
0
50
100
150
200
250
300

FIG. 28

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(71) Applicants *(for all designated States except US)*: **NEUROGEN CORPORATION** [US/US]; 35 Northeast Industrial Road, Branford, CT 06405 (US). **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DARROW, James, W.** [US/US]; 4 Dinatale Drive, Wallingford, CT 06492 (US). **DE LOMBAERT, Stephane** [US/US]; 37 Concord Drive, Madison, CT 06443 (US). **BLUM, Charles** [US/US]; 785 West Pond Meadow Rd., Westbrook, CT 06498 (US). **TRAN, Jennifer** [US/US]; 56 Barker Hill drive, Guilford, CT 06437 (US). **GIANGIORDANO, Mark** [US/US]; Building 2-14, 45 Jefferson Road, Branford, CT 06405 (US). **GRIFFITH, David, Andrew** [US/US]; 10 Barley Hill Road, Old Saybrook, CT 06475 (US). **CARPINO, Philip, Albert** [US/US]; 50 Meridian St., Groton, CT 06340 (US).

(74) Agents: **RICHARDS, John**; Ladas & Parry, 26 West 61st Sreet, New York, NY 10023 et al. (US).

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(54) Title: AMINO SUBSTITUTED PYRAZOLO[1,5,-a]-1,5-PYRIMIDINES AND PYRAZOLO[1,5-a]-1,3,5-TRIAZINES

(57) Abstract: Disclosed are compounds of the formula: (I), where R^1, R^2, R^3, R^4, R^5, R^6, and X are defined herein. These compounds are selective modulators of NPY1 receptors. These compounds are useful in the treatment of a number of CNS disorders, metabolic disorders, and peripheral disorders, particularly eating disorders and hypertension. Methods of treatment of such disorders as well as packaged pharmaceutical compositions are also provided. Compounds of the invention are also useful as probes for the localization of NPY1 receptors and as standards in assays for NPY1 receptor binding. Methods of using the compounds in receptor localization studies are given.

APPLICATION FOR UNITED STATES LETTERS PATENT IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

(Case No. U-012956-1)

(FORMERLY PROVISIONAL U012425-2)

Title: Amino Substituted Pyrazolo[1,5,-a]-1,5-Pyrimidines and Pyrazolo [1,5-a]-1,3,5-Triazines

Amino Substituted Pyrazolo[1,5,-a]-1,5-Pyrimidines and Pyrazolo[1,5-a]-1,3,5-Triazines

Related Application

This application claims priority from provisional application 60/156868 filed on September 30, 1999, which is incorporated herein by reference.

Field of the Invention

This invention relates to certain amino substituted pyrazolo[1,5,-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines, preferably those which selectively and/or potently bind mammalian neuropeptide Y (NPY) receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in treating physiological disorders associated with an excess of neuropeptide Y, especially feeding disorders, some psychiatric disorders, and certain cardiovascular diseases.

Background of the Invention

Neuropeptide Y (NPY) is a 36 amino acid peptide first isolated in 1982 and subsequently found to be largely conserved across species. It belongs to a large family of peptides that includes, among others, peptide YY (PYY) and pancreatic peptide (PP). NPY is believed to be the most abundant peptide in the mammalian brain. It is also found in sympathetic neurons, and NPY-containing fibers have been found in peripheral tissues, such as around the arteries in the heart, the respiratory tract, the gastrointestinal tract, and the genitourinary tract. Central injection of NPY elicits a multitude of physiological responses, such as stimulation of feeding, increase in fat storage, elevation of blood sugar and insulin, anxiolytic behaviors, reduction in locomotor activity, hormone release, increase in blood pressure, reduction in body temperature, and catalepsy. In the cardiovascular system, NPY is believed to be involved in the regulation of coronary tone, while in the gastrointestinal tract, PYY is reported to cause inhibition of gastric acid secretion, pancreatic exocrine secretion, and gastroinestinal motility. These effects appear to be selectively mediated by various NPY receptors which currently include the Y_1, Y_2, Y_3, Y_4, Y_5, and Y_6 subtypes, in addition to the hypothetical Y_1-like subtype. Selective peptidic agonists and

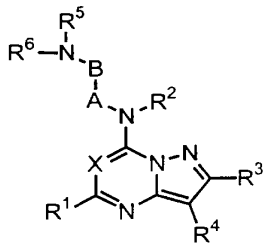
antagonists have been identified for most of the subtypes, but few selective non-peptidic antagonists have been reported. The Y_1 and Y_5 receptor subtypes appear to be involved in appetite regulation, but their relative contribution to the modulation of food intake and energy expenditure remains unclear. The discovery of non-peptidic antagonists of the Y_1 and/or Y_5 receptor provides novel therapeutic agents, that are less prone to the shortcomings of the peptide antagonists, namely, for example, poor metabolic stability, low oral bioavailability, and poor brain permeability, for the treatment of obesity and cardiovascular diseases. Recently, a few of such agents have been reported, some of which having demonstrated pharmacological efficacy in pre-clinical animal models. The present invention provides a novel class of potent non-peptidic antagonists of the NPY receptors, in particular, the Y_1 receptor.

Insofar as is known, aminoalkyl substituted pyrazolo[1,5,-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines have not been previously reported as NPY receptor antagonists useful in the treatment of feeding and cardiovascular disorders. However, this general class of compounds has been described for other uses by virtue of different mechanisms of action, e.g., as antagonists of the corticotropin releasing factor (CRF_1). For example International Patent Publication WO 98/03510 describes certain pyraazolotriazines and pyrazolopyrimidines as being of use as corticotropin releasing factors.

Summary of the Invention

Compounds that interact with the Y_1 receptor and inhibit the activity of neuropeptide Y at those receptors are useful in treating physiological disorders associated with an excess of neuropeptide Y, including eating disorders, such as, for example, obesity and bulimia, and certain cardiovascular diseases, for example, hypertension.

This invention relates to a method of treating a physiological disorder associated with an excess of neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of an amino substituted pyrazolo[1,5,-a]-1,5-pyrimidine or a pyrazolo[1,5-a]-1,3,5-triazine of the formula I:



Formula I

or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

X is N or CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2 –C_6-alkenyl, C_2 –C_6-alkynyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,

or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^7, R^7 cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

Preferred compounds of Formula I exhibit a 20-fold or more greater affinity for the NPY_1 receptor than for the CRF_1 receptor. Preferred compounds of Formula I also do not exhibit high affinity for the CRF_1 receptor.

This invention also encompasses, in additional embodiments, the novel compounds of formula I, and the salts and solvates thereof, as well as pharmaceutical formulations comprising a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers, excipients, or diluents thereof.

This invention also encompasses methods to treat physiological disorders associated with an excess of neuropeptide Y, such as eating and cardiovascular disorders, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of the formula I.

This invention also encompasses methods of selectively inhibiting binding of NPY to NPY_1 receptors, which comprises contacting a compound of formula I with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to inhibit binding of NPY to NPY_1 receptors in vitro.

Detailed Description of the Invention

The current invention includes a novel group of aminoalkyl substituted 4-amino pyrazolopyrimidines and 7-amino pyrazolo triazines, those of formula I. Preferred aminoalkyl substituted 4-amino pyrazolopyrimidines and 7-amino pyrazolo triazines bind with high affinity to the NPY_1 receptor and more preferably act as antagonists of NPY binding to the NPY_1 receptor. Preferred compounds of the invention bind with high selectivity to the NPY_1 receptor, particulary such compounds do not bind with high affinity to CRF_1 receptors. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula I with the NPY1 receptor results in the pharmaceutical utility of these compounds.

The invention further comprises methods of treating patients in need of such treatment with an amount of a compound of the invention sufficient to alter the symptoms of a eating disorder or cardiovascular disorder.

The present invention also pertains to methods of inhibiting the binding of NPY receptor ligands, such as NPY or PYY, to the NPY_1 receptors which methods involve contacting a compound of the invention with cells expressing NPY_1 receptors, wherein the compound is present at a concentration sufficient to inhibit the binding of NPY receptor Ligands to NPY_1 receptors *in vitro*. This method includes inhibiting the binding of NPY receptor ligands to NPY_1 receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of NPY receptor ligands to NPY receptors *in vitro*. The amount of a compound that would be sufficient to inhibit the binding of a NPY receptor ligand to the NPY_1 receptor may be readily determined via an NPY_1 receptor binding assay, such as the assay described in Example 94A. The NPY_1 receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of rat brain or from cells expressing cloned human NPY_1 receptors.

The present invention also pertains to methods for altering the signal-transducing activity of NPY1 nreceptors, said method comprising exposing cells expressing such receptors to an effective amount of a compound of the invention. This method includes altering the signal-transducing activity of NPY1 receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to alter the signal-transducing activity of NPY1 receptors *in vitro*. The amount of a compound that would be sufficient to alter the signal-transducing activity of NPY1 receptors may be determined via a NPY1 receptor signal transduction assay, such as the assay described in Example 93B.

The NPY1 receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the NPY1 receptor.

Radiolabeled derivatives the NPY1 receptor ligands provided by this invention are also useful for mapping the location of NPY1 receptors (e.g., in tissue sections via autoradiography) and as radiotracers for positron emission tomography (PET) imaging, single photon emission computerized tomography (SPECT), and the like, to characterize such receptors in living subjects.

In addition to compounds of Formula I, the invention also provides as preferred compounds, compounds of Formula I wherein

X is N or CH; and

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl. Such compounds will be referred to as compounds of **Formula Ia**.

Other preferred compounds of Formula I are those compounds wherein

X is N or CH; R^1 is C_1-C_6 alkyl; R^2 is H or C_1-C_6 alkyl; and

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl. Such compounds will be referred to as compounds of **Formula Ib**.

In another embodiment the invention provides compounds of Formula I, wherein

X is N or CH; R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl; R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^5 is H. Such compounds will be referred to as compounds of **Formula Ic**.

Further provided are compounds wherein:

X is N or CH; R^1 is C_1-C_6 alkyl; R^2 is H or C_1-C_6 alkyl; R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; R^4 is phenyl, mono-, di-, or tri-substituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and R^7, R^8, and R^9 are as defined for Formula I. Such compounds will be referred to as compounds of **Formula Id**.

In yet another embodiment the invention provides compounds of Formula I wherein X is N or CH; R^1 is C_1-C_6 alkyl; R^2 is H or C_1-C_6 alkyl; R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$,

C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; R^5 is H; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl. Such compounds will be referred to as compounds of **Formula Ie**.

Additionally the invention provides compounds of Formula I wherein X is N or CH; R^1 is C_1-C_6 alkyl; R^2 is H or C_1-C_6 alkyl; R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl. Such compounds will be referred to as compounds of **Formula If.**

Particularly preferred are compounds of Formula I wherein R^5 is H, and R^6 is cycloalkyl or (cycloalkyl)alkyl.(Compounds of **Formula Ig**)

For each of Formula Ia-Ig compounds that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding are preferred. Also preferred are compounds of Formula I, and Formula Ia-Ig that do not exhibit a Ki or IC_{50} of 5 micromolar or less, or more preferably that do not exhibit a Ki or IC_{50} of 1 micromolar or less, for the CRF1 receptor in an assay of CRF1 receptor binding. An assay of CRF receptor binding is given in Example 94.

In certain situations, the compounds of formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by

conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

Representative compounds of the present invention, which are encompassed by formula I, include, but are not limited to the compounds in Examples 1-87 and their pharmaceutically acceptable acid addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-(CH_2)n-COOH where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated prodrugs of the compounds of formula I. "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 the invention are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of formula I; and the like. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by formula I.

Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers. The invention includes all tautomeric forms of a compound.

By "heteroatom" in the present invention is meant oxygen or sulfur, or a nitrogen atom optionally substituted by C_1-C_6 lower alkyl, C_1-C_6 arylalkyl, C_1-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_8 alkanoyl, C_1-C_6 sulfonyl.

By "alkyl", "lower alkyl", or "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "cycloalkyl", or "C_3-C_{10} cycloalkyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi-, or polycyclic ring system, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

By "(cycloalkyl)alkyl", "lower (cycloalkyl)alkyl", or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl in the present invention is meant a straight or branched alkyl substituent formed of 1 to 6 carbon atoms attached to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, and the like.

The term "C_2-C_6 alkenyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or branched arrangement and containing one or more unsaturated carbon-carbon double bonds which may occur in any stable point along the chain, such as, for example, ethenyl, allyl, isopropenyl, and the like.

By "cycloalkenyl" or "C_3-C_{10} cycloalkenyl" in the present invention is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi, or polycyclic ring system having 3-10 carbon atoms and containing one or more carbon-carbon double bonds which may occur in any stable point in the ring, such as, for example, cyclopentenyl, cyclohexenyl, or cycloheptenyl.

The term "C_2-C_6 alkynyl" in the present invention means hydrocarbon chains having 2 to 6 carbons in a straight or branched arrangement and containing one or more unsaturated carbon-carbon triple bonds which may occur in any stable point along the chain, such as, for example, ethynyl, propargyl, and the like.

The term "aryl" in the present invention means a monocyclic or bicyclic aromatic group having preferably 6 to 10 carbon atoms, such as, for example, phenyl or naphthyl.

The term "heteroaryl" in the present invention means an aryl group in which one or more of the ring(s) carbon atoms have been replaced with a heteroatom. Such groups preferably have

4 to 10 carbon atoms and 1 to 4 heteroatoms, such as, for example, pyridyl, pyrimidinyl, triazinyl, imidazolyl, oxazolyl, isoxazolyl, indolyl, pyrrolyl, pyrazolyl, quinolinyl, isoquinolinyl, thiazolyl, benzothiadiazolyl, triazolyl, triazinyl, pyrazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, tetrazolyl.

The term "heterocyclyl", "heterocycle"or "heterocycloalkyl" in the present invention means a saturated or partially saturated heteroaryl group.

By "C_1-C_6 arylalkyl" or "C_1-C_6 heteroarylalkyl" in the present invention is meant a branched or straight-chain alkyl group having 1-6 carbon atoms and substituted on one of the carbon atoms by an optionally substituted aryl or heteroaryl ring, such as, for example, benzyl, phenethyl, methylpyridyl, ethylpyridyl, and the like.

By "C_5-C_8 arylcycloalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms and fused to an aryl group, such as, for example, 1,2,3,4 tetrahydronaphthalenyl, 2,3-dihydrobenzothienyl, or 2,3-dihydobenzofuranyl.

By "C_5-C_8 heteroarylcycloalkyl" in the present invention is meant cycloalkyl groups having 5-8 carbon atoms fused to a heteroaryl group, such as, for example, 1,2,3,4 tetrahydroquinolyl, 2,3-dihydrobenzothienyl, 2,3-dihydobenzofuranyl, or indolinyl.

By "alkoxy", "C_1-C_6 alkoxy", or "C_1-C_6 alkyloxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By "cycloalkoxy", "C_3-C_{10} cycloalkoxy", or "C_3-C_{10} cycloalkyloxy" in the present invention is meant a group formed by an oxygen atom attached to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, or cycloheptoxy.

By "(cycloalkyl)alkyloxy", "(C_3-C_{10} cycloalkyl) C_1-C_6 alkoxy", or "(C_3-C_{10} cycloalkyl) C_1-C_6 alkyloxy" in the present invention is meant a group formed by an oxygen atom attached to a 1-6 carbon chain linked to a mono-, bi, or polycyclic ring system having 3-10 carbon atoms, such as, for example, cyclopropylmethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cycloheptylmethyloxy, and the like.

By "C_3-C_6 aminocarbocycle" is meant a cyclic amino group formed by a nitrogen contained in a ring having 3 to 6 carbon atoms, such as, for example, azetidino, pyrrolidino, piperidino, perhydroazepino.

By "C_2-C_5 aminoheterocycle" is meant a cyclic amino group formed by a nitrogen contained in a ring having 2 to 5 carbon atoms and one other heteroatom, such as, for example, morpholino, thiomorpholino, piperazino.

By the terms "halo" or "halogen" in the present invention is meant fluoro, chloro, bromo, and iodo.

"Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms substituted with 1 or more halogens.

The term "C_2-C_8 alkanoyl" means an acyl group with 2 to 8 carbon atoms in a linear, branched, or C_3-C_{10} cycloalkyl arrangement, optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, trifluoromethyl, OR^7, NR^8R^9, $CONR^8R^9$, $COOR^7$, or CN.

The term "C_1-C_6 alkyl sulfonyl" means an alkylsulfonyl group containing 1 to 6 carbon atoms in a linear, branched, or C_3-C_7 cycloalkyl arrangement.

The term "substituted" means that one or more hydrogen on the designated atom is replaced by the specified group, provided that the valence on the designated atom is not exceeded, and that a chemically stable compound results from the substitution.

A stable compound is defined herein as one that can be isolated, characterized, and tested for biological activity.

The term "oxo" (i.e. =O) indicates that two geminal hydrogen atoms are replaced by a double-bond oxygen group.

The term "hydroximino" (i.e. =N-OH)) indicates that two geminal hydrogen atoms are replaced by a double-bond nitrogen atom substituted with a hydroxyl group.

The term "C_1-C_6 alkoximino" (i.e. =N-O-Alkyl) indicates that two geminal hydrogen atoms are replaced by a double-bond nitrogen atom substituted with a C_1-C_2 alkoxy group, such as, for example, methoximino (=N-OMe).

In the present invention, the term "potent" in the context of NPY1 receptor antagonists qualifies a binding affinity with a Ki of less than 10 micromolar, preferably less than 1 micromolar, and more preferably less than 100 nanomolar in the human NPY1 binding assay.

In the present invention, the term "selective" in the context of NPY1 receptor antagonists qualifies a binding affinity with a Ki in the human NPY1 binding assay that is 10-fold or 20-fold, preferably 100-fold, and more preferably 1000-fold, less than the Ki of the same compound measured in another receptor binding assay, in particular the NPY_5 and $CRF1_1$ receptor binding assays. Binding assays for the NPY_5 and $CRF1_1$ receptors have been described, for example, in *J. Clin. Invest.*, 102, 2136 (**1998**) and in *Endocrinology* 116, 1653 (**1985**), respectively. A CRF1 receptor binding assay is also given in Example 94.

As the compounds of formula I are selective antagonists of the Y1 receptor, they are of value in the treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of neuropeptide Y. Thus, the invention provides methods for the treatment or prevention of a physiological disorder associated with an excess of neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof. The term "physiological disorder associated with an excess of neuropeptide Y" encompasses those disorders associated with an inappropriate stimulation of neuropeptide Y receptors, regardless of the actual amount of neuropeptide Y present locally. These physiological disorders may include: disorders or diseases pertaining to the heart, blood vessels or the renal system, such as vasospasm, heart failure, shock, cardiac hypertrophy increased blood pressure, angina, myocardial infarction, sudden cardiac death, arrhythmia, peripheral vascular disease, and abnormal renal conditions such as impaired flow of fluid, abnormal mass transport, or renal failure; conditions related to increased sympathetic nerve activity for example, during or after coronary artery surgery, and operations and surgery in the gastrointestinal tract; cerebral diseases and diseases related to the central nervous system, such as cerebral infarction, neurodegeneration, epilepsy, stroke, and conditions related to stroke, cerebral vasospasm and hemorrhage, depression, anxiety, schizophrenia, and dementia; conditions related to pain or nociception; diseases related to abnormal gastrointestinal motility and secretion, such as different forms of ileus, urinary incontinence, and Crohn's disease; abnormal drink and food intake disorders, such as obesity, anorexia, bulimia, and metabolic disorders; diseases related to sexual dysfunction and reproductive disorders; conditions or disorders associated with inflammation; respiratory diseases, such as asthma and conditions related to asthma and

bronchoconstriction; and diseases related to abnormal hormone release, such as leutinizing hormone, growth hormone, insulin, and prolactin.

Pharmaceutical Preparations

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachid oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachid oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said

partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 50 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 3 g per patient per day), although higher amounts , for example up to 140 mg./kg/day may be appropriate in some circumstances. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most eating disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of stress and depression a dosage regimen of 1 or 2 times daily is particularly preferred.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (*Journal of Chromatography B* **1996,** *677*, 1-27).

Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (*Drug Metabolism and Disposition* **1998,** *26*, 1120-1127).

As discussed above, preferred compounds of the invention exhibit good activity in standard *in vitro* NPY receptor binding assays, specifically the assay as specified in Example 93A, which follows. References herein to "standard *in vitro* NPY receptor binding assay" are intended to refer to that protocol as defined in Example 93A which follows. Generally preferred compounds of the invention exhibit a K_i of about 1 micromolar or less, still more preferably and K_i of about 100 nanomolar or less even more preferably an K_i of about 10 nanomolar or less or even 1 nanomolar or less in such a defined standard *in vitro* NPY receptor binding assay as exemplified by Example 93A which follows.

In appropriate case, the compounds of the invention may be employed in combination with other active agents. The invention therefore also provides pharmaceutical combination compositions comprising a therapeutically effective amount of a composition comprising: (a) first compound, said first compound being a compound as described above a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle or diluent. . To this end therefore the invention also provides a kit comprising: (a) first compound, said first compound being a compound as described above, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; and (c) means for containing said first and second unit dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

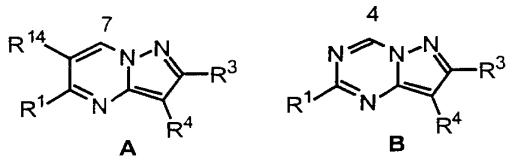
Synthetic Schemes

Preparation of Amino Substituted Pyrazolo[1,5,-a]-1,5-Pyrimidines and Pyrazolo[1,5-a]-1,3,5-Triazines Derivatives

An illustration of preparation methods of compounds of the present invention is given in the Schemes below. In particular displacement of a leaving group Z, as in formula **10** (Scheme 1) by the appropriate substituted amine provides a method to convert the heterocyclic cores of the present invention, i.e. aryl or heteroaryl substituted pyrazolo[1,5,-a]-1,5-pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines, into compounds that potently interact with the NPY1 receptor. Such transformations may require several consecutive chemical steps. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention. The disclosures of all articles and references mentioned in this application, including patents, are incorporated herein by reference.

Unless otherwise specified the variable R^1, R^2, R^3, R^4, R^5, R^6, and X are as defined for Formula I.

One general approach is to convert a heterocyclic core **A** and or a heterocyclic core **B**



A **B**

to a compound that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, wherein

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN;

by substituting the 7-position of the heterocyclic core **A** or the 4-position of the heterocyclic core **B** with a diamine group $-N[R^2]-A-B-N[R^6]-R^5$

wherein:

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,
or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^7, R^7 cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

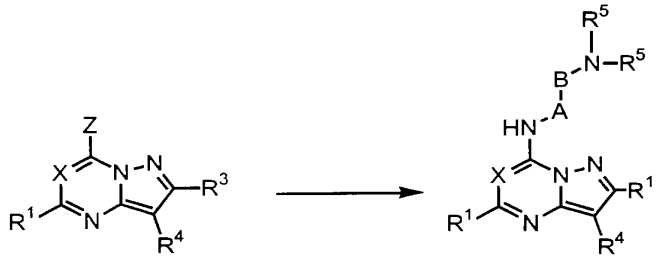
R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle; and

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H.

More specifically the following schemes may be used.

SCHEME 1



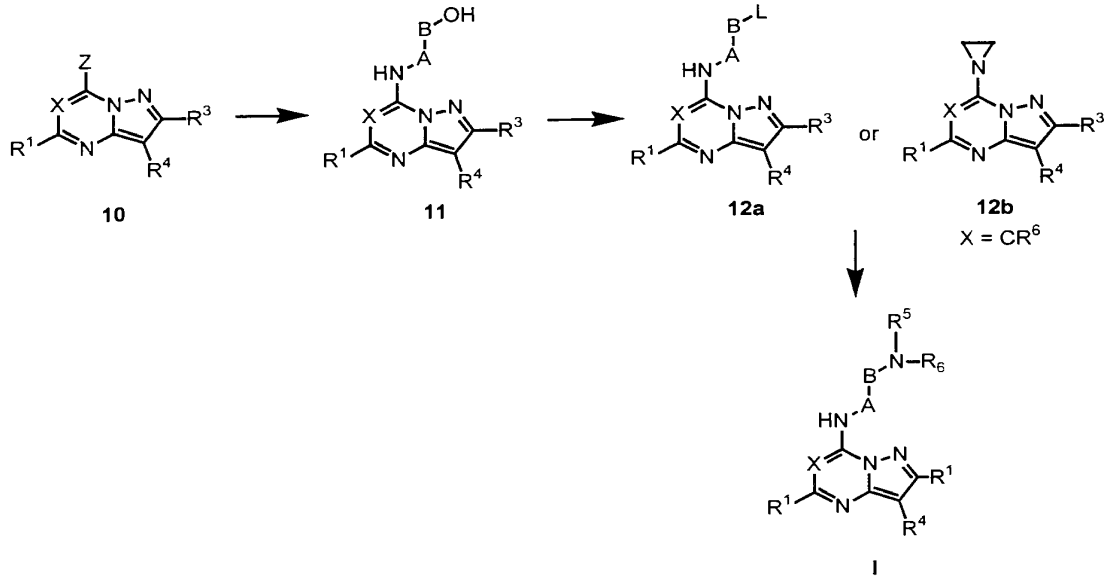
10 I

As illustrated in Scheme 1, compounds of formula I can be prepared from intermediate compounds of formula **10**, where Z is halogen (preferably chloro or bromo), alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy, and X, R^1, R^3 and R^4 are defined above, using the procedures outlined below.

Compounds of formula **10** react with an amine of formula H_2N-A-B-N[R^6]-R^5, where A,B, R^5 and R^6 are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C to generate compounds of formula I. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or

toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

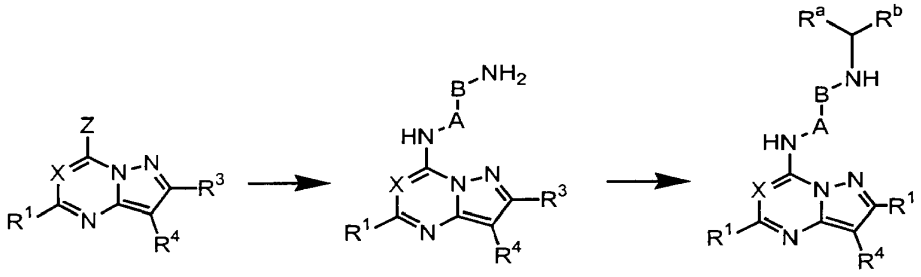
SCHEME 2



Alternatively, as shown in Scheme 2, compounds of formula I can be obtained by first reacting a compound of formula **10** with an amino alcohol of formula H_2N-A-B-OH, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C to generate intermediates of formula **11**. Reacting a compound of formula **11** with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from –78°C to 250C°C to afford products of formula **12a** (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy) or **12b** when A and B are both CH_2 and X is CR^{14}. Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, PBr_5., CCl_4/PPh_3. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl

aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from –20°C to 100C°C. Compounds of formula **12a** or **12b** can then be reacted with an amine of formula $HN[R^6]$-R^5, where R^5 and R^6 are defined as above, to give a compound of formula I. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

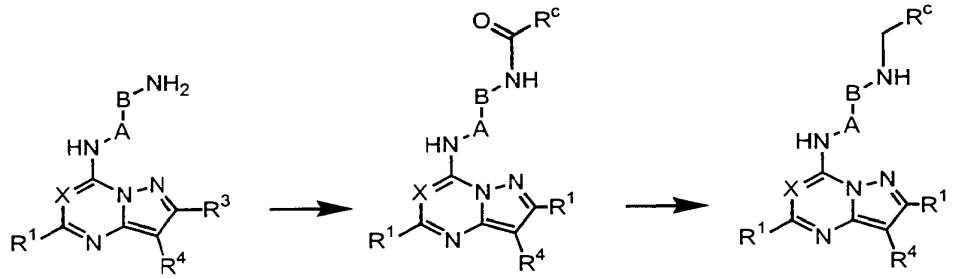
SCHEME 3



10 **13** **Ia**

A subset of compounds of formula I, described under formula Ia, can be obtained by first reacting a compound of formula **10** with a diamine of formula H_2N-A-B-NH_2, where A and B are defined as above, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C to generate intermediates of formula **13**. Reaction of a compound of formula **13** with an aldehyde or ketone of Formula R^a-C=O-R^b in the presence of a reducing agent provides a compound of formula Ia, where the grouping R^a-CH-R^b corresponds to R^5 in formula I, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -78C°C to 100°C.

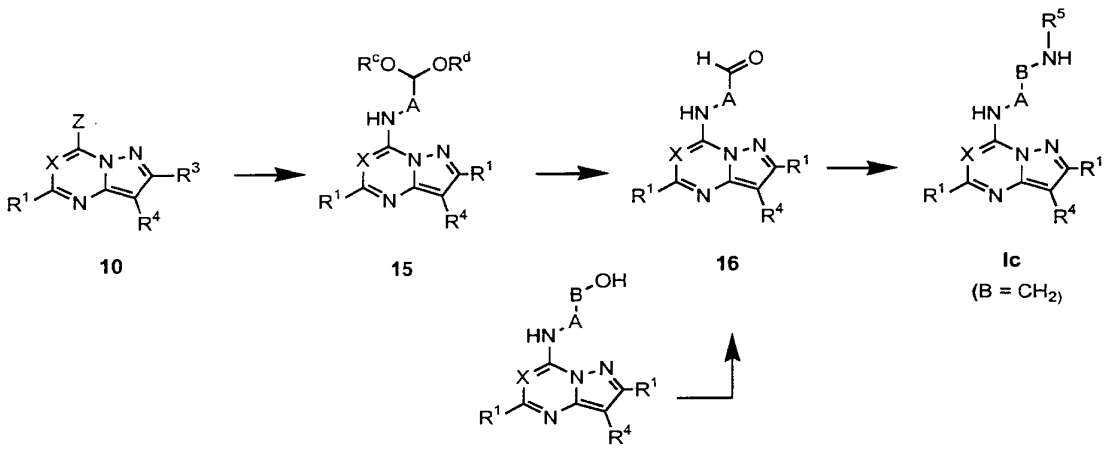
SCHEME 4



13 14 Ib

Alternatively, a subset of compounds of formula I, described under formula Ib, can be obtained by first reacting a compound of formula **13** with an activated acid of formula R^c-C=O-Z, where Z is halo (preferably chloro), O-acyl (preferably O-C=O-R^c), in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78 °Cto 250C°C to generate an amide intermediate of formula **14**. Reaction of a compound of formula **14** with a reducing agent provides a compound of formula Ib, where the grouping R^c-CH_2 corresponds to R^5 in formula I, as defined above. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -78°C to 100°C.

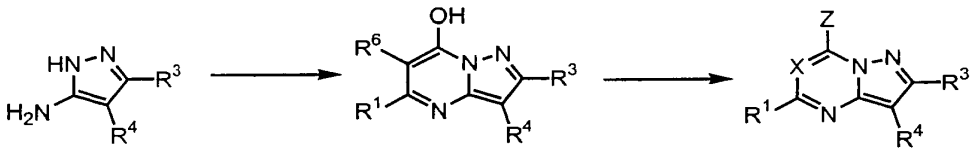
SCHEME 5



Alternatively, a subset of compounds of formula I, described under formula Ic, can be obtained by first reacting a compound of formula **10** with an amine of formula H_2N-A-$CH(OR^c)(OR^d)$, where A is defined above, and R^c and R^d are C_1-C_6 lower alkyls or, taken together, complete a ketal group, such as, for example a dioxane or dioxolane group, in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250C°C to generate compounds of formula **15**. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), arylamines (preferably 4-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or

toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Compounds of formula **15** react with a protic acid in the presence or absence of an inert solvent at reaction temperatures ranging from -78°C to 250°C, followed by aqueous work-up to generate compounds of formula **16**. Inert solvents may include, but are not limited to dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes (1-10 carbons and 1-10 halogens) (preferably dichloromethane). Protic acids include, but are not limited to, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, methane sulfonic acid. Alternatively, compounds of formula **16** can be obtained by oxidation of compounds of formula **11** where B= CH_2. Oxidizing agents include, but are not limited to, transition metal oxides, such as CrO_3 or MnO_2, pyridine-chromium complexes, such as $CrO_3.C_5H_5N$, pyridinium dichromate or pyridinium chlorochromate, or an oxalyl chloride-DMSO-triethylamine reagent (Swern oxidation). Compounds of formula **16** react with amines of formula $H_2N\text{-}R^5$, where R^5 is defined above, in the presence of a reducing agent in the presence or absence of an inert solvent in the presence or absence of a protic acid at temperatures ranging from –78°C to 100°C, to give compounds of formula **Ic**. Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane (preferably complexed with dimethyl sulfide or tetrahydrofuran), dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides (such as triethoxyaluminum hydride), dialkyl aluminum hydrides (such as di-isobutyl aluminum hydride), alane (preferably complexed with dimethyl amine). Inert solvents may include, but are not limited to, alkyl alcohols (1-6 carbons) (preferably methanol, ethanol, or tert-butanol), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 6



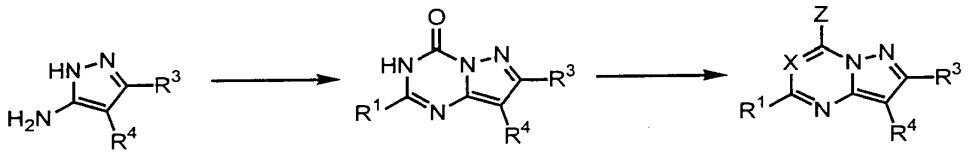
22 **23a** **10**

X = CR^6

When X is CR^{14}, as defined above, compounds of formula **10** may be obtained from compounds of formula **22**. Compounds of formula **22** can be reacted with compounds of formula R^1-C=O-CH(R^{14})-C=O-R^c, where R^1 and R^{14} are defined above, and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base in an inert solvent at reaction temperatures ranging from –50C°C to 250C°C to afford compounds of formula **23a**. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Compounds of formula **23a** can then be reacted with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from –78C°C to 250°C to afford products of formula **10** (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is CR^{14}). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or

anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

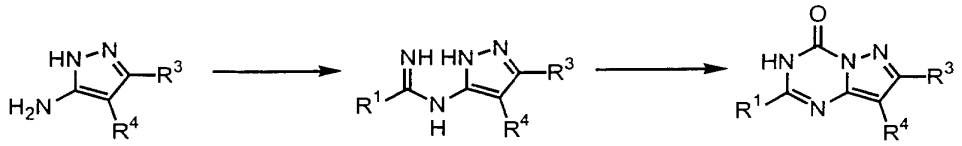
SCHEME 7



When X is N, compounds of formula **22** can be reacted with compounds of formula R^1-C=N($COOR^g$)-OR^f, where R^1 is defined above, and R^g is lower alkyl (1-6 carbons), and R^f is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence or absence of a base in an inert solvent at reaction temperatures ranging from –50°C to 250°C to afford compounds of formula **23b**. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably

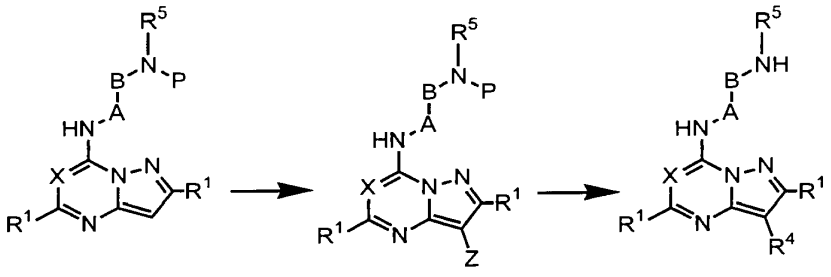
acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), heteroaromatic hydrocarbons (preferably pyridine). Compounds of formula **23b** can then be reacted with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from –78C to 250C to afford products of formula **10** (where Z is halogen, alkane sulfonyloxy, aryl sulfonyloxy or haloalkane sulfonyloxy and X is N). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3, or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (preferably methanesulfonyl chloride or methanesulfonic anhydride), aryl sulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride), or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), anilines (preferably N-dimethyl aniline), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

SCHEME 8



Alternatively, compounds of formula **23b** can be obtained by first reacting compounds of formula **22** with compounds of the formula R^1-(C=NH)-OR^h, where R^1 is defined above and R^g is a lower alkyl group (preferably methyl or ethyl), in the presence or absence of an acid in an inert solvent to give an intermediate of formula **24**. Compounds of formula **24** react with a compound of formula R^i-C=O-R^j, where R^i and R^j are each or independently lower alkoxy (preferably methoxy or ethoxy), 1-imidazolyl, halo, aryloxy (preferably 4-nitrophenoxy) in the presence or absence of an inert solvent to afford compounds of formula **23b**. Bases may include, but are not limited to, alkali metals (preferably sodium), alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

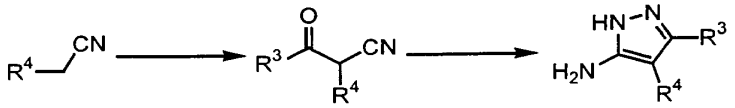
SCHEME 9



17 18 I

Compounds of formula I can also be prepared from compounds of formula **17** (prepared using the methods applicable to the synthesis of compounds of formula I), where P is H or an appropriate amino protecting group. Such groups, known in the art of organic synthesis for the protection of amines, include those listed in "Protective Groups in Organic Synthesis", by Greene and Wuts [John Wiley & Sons, NY, **1991**]. Examples of amine protecting groups include, but are not limited to, acyl types (such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl), carbamate types (such as benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenymethyloxycarbonyl, allyloxycarbonyl, and 2,2,2-trichloroethyloxycarbonyl), alkyl types (such as benzyl and triphenylmethyl). Reacting compounds of formula **17** with a halogenating agent provides compounds of formula **18** where X is Br, Cl, or I. Compounds of formula **18** react with a compound of formula R^4M (where M is alkali metal, ZnCl, ZnBr, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$, copper halides, $B(OH)_2$, B(O-lower alkyl)$_2$, or Sn(lower alkyl)$_3$) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvent at temperatures ranging from –100°C to 200°C to give compounds of formula I (or their N-protected forms which can then be deprotected). Similar conditions have been described in WO 98/54093. Those skilled in the art will recognize that the reagents R^4M may be generated in situ. Organometallic catalysts include but are not limited to, palladium phosphine complexes (such as $Pd(PPh_3)_4$), palladium halides or alkanoates (such as $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$), or nickel complexes (such as $NiCl_2(PPh_3)_2$). Bases may include, but are not limited to, alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkali metal carbonates or bicarbonates, alkali metal hydroxides, alkali metal phosphates, or trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 10

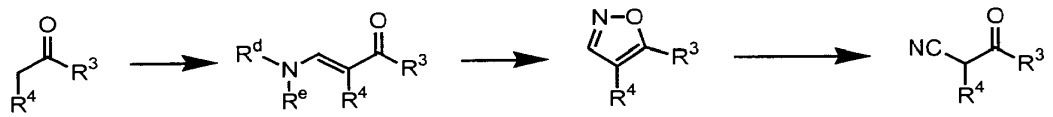


20 **21** **22**

Compounds of formula **22** may be obtained from compounds of formula **20**, where R^4 is defined as above. Compounds of formula **20** are reacted with compounds of formula R^3-C=O-R^c, where R^3 is defined above and R^c is halogen, cyano, lower alkoxy (1-6 carbons), or lower alkanoyloxy (1-6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from –78°C to 200°C to afford compounds of formula **21**. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Alternatively, compounds of formula **20** may be reacted with a solvent of formula R^3-C=O-R^c, where R^3 is defined above and R^c is lower alkoxy (1-6 carbons), in the presence of an alkali metal (preferably sodium) at reaction temperatures ranging from –78°C to 200°C to afford compounds of formula **21**. Compounds of formula **21** may be reacted with hydrazine (hydrate or hydrochloride salt) in an inert solvent, at reaction temperatures ranging from 0°C to 200°C, preferably 70°C to 150°C, to afford compounds of formula **22**. Inert solvents may include, but are not limited to, water, lower alkanoic acids (preferably formic, acetic, or trifluoro acetic acid), alkyl alcohols (1-8 carbons) (preferably methanol or ethanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), cyclic ethers

(preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

SCHEME 11



24 **25** **26** **21**

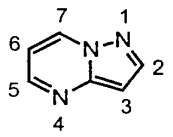
Alternatively, compounds of formula **21** can be obtained by first reacting compounds of formula **24** with dialkyl formamide dialkyl acetal of formula $(R^dR^e)N\text{-}CH(OR^f)_2$ where R^d, R^e, and R^f are each or independently C_1-C_6 lower alkyl (preferably methyl) in the presence or absence of an inert solvent at reaction temperatures ranging from 0°C to 250°C, preferably between 70C°C and 150°C to provide compounds of formula **25**. Inert solvents may include, but are not limited to, lower alkanenitriles (1-6 carbons) (preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), or haloalkanes with 1-10 carbons and 1-10 halogens (preferably dichloromethane). Compounds of formula 25 can be reacted with hydroxylamine salt (preferably hydrochloride) in the presence or absence of an inert solvent at reaction temperatures ranging from 0°C to 250°C, preferably between 70C°C and 200°C to provide oxazoles of formula **26**. Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene). Oxazole intermediates of formula **26**

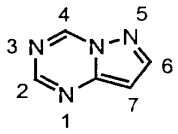
can be reacted with a base in the presence or absence of an inert solvent at reaction temperatures ranging from 0C°C to 200°C. Bases may include, but are not limited to, alkali hydroxides (preferably sodium or potassium hydroxide), alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1-6 carbons) (preferably sodium methoxide, sodium ethoxide, or sodium tert-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis-(trialkylsilyl)amides (preferably lithium or sodium (trimethylsilyl)amide), trialkylamines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine), bicyclic amidines (preferably DBU), or heteroaromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1-8 carbons) (preferably methanol, ethanol, or tert-butanol), lower alkanenitriles (1-6 carbons) (preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethyl formamide), N,N-dialkylacetamides (preferably dimethyl acetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene).

EXAMPLES

The following examples listed in the TABLE are provided to describe the invention in further details. These examples can be prepared by one or more of the above-mentioned method and are intended to illustrate and not to limit the invention.

The numbering system used to describe the compounds of the present invention is as follows:





Commercial reagents were used without further purification. THF refers to tetrahydrofuran. LDA refers to lithium diisopropylamide and DBU refers to 1,8-diazabicyclo[5.4.0]undec-7-ene. Room or ambient temperature refers to 20°C to 25°C. Concentration implies the use of a rotary evaporator. TLC refers to thin layer chromatography.

Mass spectral data were obtained either by CI or APCI methods. Other commonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, Bu is butyl, iBu is isobutyl (CH_2-$CHMe_2$), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, cHex is cyclohexyl, Py is pyridyl, MeOH means methanol, EtOH means ethanol, EtOAc means ethyl acetate, Et_2O means diethyl ether, CH_2Cl_2 means methylene chloride, DMSO means dimethyl sulfoxide, NMP means N-methyl pyrrolidone, THF means tetrahydrofuran, DMF means dimethyl formamide, EX means example,

EXAMPLE 1

Preparation of 7-(2-(cyclohexylamino)ethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine

(formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R3 is CH_3, R^4 is 2,6-dimethyl-4-chlorophenyl, R^5 is cyclohexyl)

A. 4-Bromo-3,5-dimethyl chlorobenzene

Slurry 2,6-dimethyl-4-chloroaniline hydrochloride (23g, 193.11 g/mol) in CH_2Cl_2 (100 ml) and wash with saturated $NaHCO_3$ to generate the free base. Dry over Na_2SO_4, filter and evaporate down to a violet oil. Slurry up in 120 mL 6.0 N H_2SO_4 and stir vigorously at ambient temperature to break up larger pieces of solid. Cool to 0°C in an ice/water bath, then portionwise over 15 min add a clear colorless solution of $NaNO_2$ in 50 mL H_2O. Maintain temperature 15°C over course of addition, stirring under dry N_2. After 1 hour, carefully pour the cold reaction solution (solution A) into a second solution (solution B) containing 31.7 g CuBr in 33 mL aqueous HBr (48%) at ambient temperature. Let stand at ambient temperature until gas evolution ceases, then heat to 110°C under N_2 while stirring. Stir for 3 h, then cool to rt. Extract the aqueous layer with a (2:1) mixture of hexanes and Et_20 (2 x 500 mL), then dry the combined organic layers over Na_2SO_4, filter and evaporate down to a brown oil. Triturate the oil with hexanes (100 mL), filter out the remaining solids and wash with copious amounts of hexanes.

Evaporate the hexane layers to concentrate then flush through a pad of silica to remove baseline material, using hexanes as eluent. Evaporate to a clear colorless oil (13.5g).

B. 4-Chloro-2,6-dimethyl benzaldehyde

Dissolve 4-bromo-3,5-dimethyl chlorobenzene (6.5 g) in 50 mL anhydrous THF and cool to –78°C (dry ice/acetone) under N_2. Dropwise over 5 min add a solution of butyllithium (12.50 mL, 2.5M in hexanes) to the stirring solution of aryl bromide at –78°C. After 2 h, dropwise add anhydrous DMF (5.0 mL) to the orange/red reaction solution and allow to warm to ambient temperature overnight while stirring under N_2. Evaporate the yellow solution down to a yellow oil and partition between H_2O (100 mL) and CH_2Cl_2 (100 mL). Extract the aqueous layer once with CH_2Cl_2, then pool the organic layers and dry over Na_2SO_4, filter and evaporate down to 5.0 g of yellow oil. Use without further purification. LCMS = 169.6 (MH^+)

C. 4-Chloro-2,6-dimethyl benzyl alcohol

Dissolve 4-chloro-2,6-dimethyl benzaldehyde (5.0 g, 168.64 g/mol) in 100 mL dry MeOH. Cool to 0°C while stirring under N_2. Portionwise add powdered $NaBH_4$ (0.76g, 37.85 g/mol) over 5 min. Stir at 0°C for 2 h, monitoring by TLC until aldehyde consumed, then evaporate to a yellow oil. Add H_2O (50 mL) and bring to pH 7.0 by addition of saturated NH_4Cl. Extract the neutral aqueous layer with CH_2Cl_2 (3 x 75 mL) and dry the pooled organic layers over Na_2SO_4. Filter and concentrate to a yellow oil. Flush through a pad of silica to remove baseline material, then evaporate to a yellow solid (3.0 g) which can be used without further purification. LCMS = 171.6 (MH^+), 169.6 (M^-)

D. 4-Chloro-2,6-dimethyl phenyl acetonitrile

Dissolve 4-chloro-2,6-dimethyl benzyl alcohol (2.8g, 170.66 g/mol) in CH_2Cl_2 (25 mL) and cool to 0°C under N_2. Dropwise add thionyl chloride (2.4 mL, 3.90 g, 118.9 g/mol) in 10 mL CH_2Cl_2 while stirring under N_2. After 2 h, monitoring by TLC (alcohol Rf=0.35, chloride Rf=1.0; using 20% EtOAc / 80% hexanes as eluent), quench the reaction carefully by addition of

saturated $NaHCO_3$ (100 mL) and stir until gas evolution ceases. Separate layers, then extract the aqueous layer with CH_2Cl_2 (100 mL). Pool the organic layers, dry over Na_2SO_4, filter and evaporate to a pale yellow oil. Take up in DMSO (25 mL), add solid NaCN (1.25 g, 49.011 g/mol) and heat to 60°C while stirring under N_2. Stir 2 h until chloride consumed (TLC; chloride Rf=1.0, nitrile Rf=0.6; using 20% EtOAc / 80% hexanes as eluent), then cool to rt. Add 2.0 N NaOH (150 mL) and stir until orange precipitate forms, then filter and wash solid with H_2O. Dissolve solid in CH_2Cl_2, wash with H_2O, the dry over Na_2SO_4. Filter the organic layer and evaporate to an orange oil which crystallizes upon standing at ambient temperature. (2.3 g). LCMS = 180.2 (MH^+), 178.2 (M^-).

E. 2-(4-Chloro-2,6-dimethylphenyl)-3-oxobutanenitrile

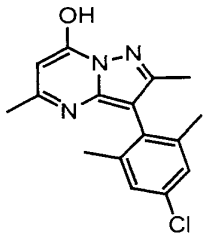
Dissolve 4-chloro-2,6-dimethyl phenyl acetonitrile (2.3 g, 179.2 g/mol) in 15 mL EtOAc and add sodium metal (0.35 g, pea-sized fragments). Heat to reflux (90°C bath temperature) under N_2 overnight. Evaporate down to solid and slurry up in Et_2O (100 mL); stir vigorously to break up fragments. Filter and wash solid with copious amounts of Et_2O. Dissolve solid in H_2O to form a clear yellow solution, and add 1.0 N HCl (100 mL) to pH 1. Extract the resulting cloudy solution with CH_2Cl_2 (3 x 100 mL) until aqueous layer is clear. Pool and dry the organic layers over Na_2SO_4, filter and evaporate to yellow oil (1.8g). TLC: Rf=0.2 using 20% EtOAc / 80% hexanes as eluent. LCMS = 222.3 (MH^+); 220.2 (M^-)

F. 5-Amino-4-(4-chloro-2,6-dimethylphenyl)-3-methylpyrazole

Dissolve anhydrous hydrazine (0.91g, 0.90 mL) in 20 mL toluene. Add glacial acetic acid (2.25 mL) and allow to stand at ambient temperature for 10 min until solution becomes cloudy white. Add a solution of 2-(4-chloro-2,6-dimethylphenyl)-3-oxobutanenitrile in 10 mL toluene, rinsing out the ketonitrile flask with an additional 5 mL toluene. Heat to reflux under N_2 (130°C) with Dean-Stark trap attached. Water will begin to accumulate after 10 min or so. After 2 h, evaporate down and partition between 1.0 N NaOH (100 mL) and EtOAc (100 mL). Extract aqueous layer with EtOAc (2 x 100 mL), then pool the organic layers and dry over Na_2SO_4.

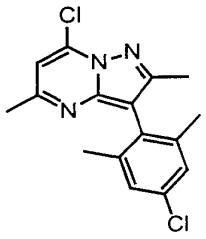
Filter and evaporate to yellow oil (1.75 g). Use without further purification. LCMS = 236.5 (MH^+); 234.5 (M^-).

G. 7-Hydroxy-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a]pyrimidine



Dissolve 5-amino-4-(4-chloro-2,6-dimethylphenyl)-3-methylpyrazole in 20 mL glacial acetic acid at ambient temperature, and add ethyl acetoacetate (2.0 mL, 1.99 g). Heat to reflux (130°C) under N_2 overnight. Evaporate down to concentrate and add 200 mL Et2O to precipitate out product. Stir at ambient temperature for 1 hour, then filter and wash the resulting white solid (1.25 g) with copious amounts of Et_2O. LCMS = 302.2 (MH^+); 300.2 (M^-).

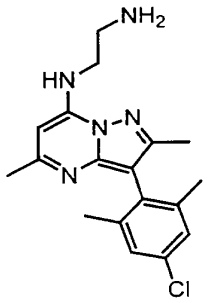
H. 7-Chloro-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a]pyrimidine



Slurry 7-hydroxy-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine in 10 mL $POCl_3$ and reflux at 130°C under N_2. After 2 h, monitoring by TLC (alcohol Rf=0.5, chloride Rf=1.0; EtOAc as eluent), quench the reaction carefully at ambient temperature by diluting with 50 mL CH_2Cl_2 and pouring slowly into non-stirring saturated $NaHCO_3$. Adjust stirring speed to control rate of quenching of residual $POCl_3$ and stir until gas evolution ceases. Separate the layers and extract the aqueous layer with CH_2Cl_2 (2 x 50 mL).

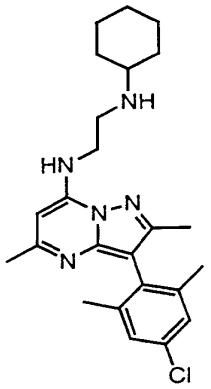
Pool the organic layers and dry over Na_2SO_4. Filter and evaporate to yellow oil, which is used directly without further purification.

I. 7-(2-aminoethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine



Dissolve 7-chloro-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine in 25 mL CH_3CN, then add excess ethylenediamine (5 mL) and heat to 80°C for 3-6 h under N_2 with attached reflux condenser. (TLC; product diamine Rf=0.5, aryl chloride Rf=1.0; [10% (2.0M NH_3 in MeOH) / 90% CH_2Cl_2] as eluent). Cool to ambient temperature and evaporate to yellow oil. Partition between CH_2Cl_2 (50 mL) and 1.0 N NaOH (50 mL), and extract aqueous layer 2 x 30 mL CH_2Cl_2. Pool organic layers, dry over Na_2SO_4, filter and evaporate to yellow-white foam (1.25 g). Use without further purification. LCMS = 344.4 (MH^+); 342.3 (M^-).

J. 7-(2-(Cyclohexylamino)ethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo[1,5-a] pyrimidine



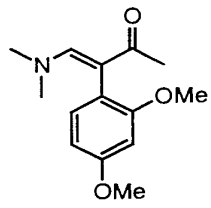
Dissolve 7-(2-aminoethylamino)-2,5-dimethyl-3-(4-chloro-2,6-dimethylphenyl)-pyrazolo [1,5-a] pyrimidine (0.183g, 5.4 x 10^{-4} mol, 339.2 g/mol) in dichloroethane (5 mL) and add cyclohexanone (100.12 g/mol) and sodium triacetoxyborohydride (0.172 g, 211.94 g/mol). To the resultant slurry, add glacial acetic acid (0.032 mL, 5.4 x 10^{-4} mol) and stir at ambient temperature under N_2 for 3 h. Partition between CH_2Cl_2 (3 mL) and 1.0 N NaOH (10 mL), then separate the layers and chromatograph the CH_2Cl_2 layer using [10% (2.0M NH_3 in MeOH) / 90% CH_2Cl_2] as eluent. Obtained 0.16 g white solid-foam upon evaporation.

EXAMPLE 2

Preparation of 7-(2-cyclopentylamino)ethylamino)-3-(2,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

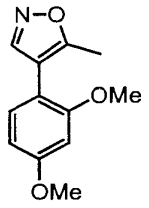
(formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,4-dimethoxyphenyl, R^5 is cyclopentyl)

A. (3E)-3-(2,4-dimethoxyphenyl)-4-(dimethylamino)but-3-en-2-one



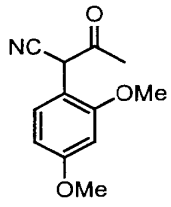
Dissolve 1-(2,4-dimethoxyphenyl)acetone (1.0 g, 5.15 mmol, 194.23 g/mol) in DMF-diethyl acetal (4.5 mL, 25.7 mmol, 147.22 g/mol) and stir under N_2 at 100°C overnight. TLC using 20% EtOAc / 80% hexanes; (ketone Rf = 0.25, product Rf = 0.0). Evaporate to thick oil, dissolve in EtOAc (25 mL) and wash with H_2O (3 x 25 mL). Extract pooled H_2O layers with EtOAc. Dry pooled organic layers over Na_2SO_4, filter and evaporate to thick oil which solidifies upon standing at ambient temperature (0.98 g). Use without further purification. LCMS = 250.2 (MH^+); 248.2 (M^-).

B. 4-(2,4-Dimethoxyphenyl)-5-methyl-isoxazole



Dissolve (3E)-3-(2,4-dimethoxyphenyl)-4-(dimethylamino)but-3-en-2-one (5.1 g, 20.6 mmol) in EtOH (50 mL) and add NH_2OH•HCl (3.05 g, 44.0 mmol). Heat to reflux under N_2 for 20 min. Cool and evaporate to red-brown oil. Dissolve in CH_2Cl_2, dry over Na_2SO_4, filter and concentrate to red-brown oil (4.4 g). Use without further purification. LCMS = 220.2 (MH^+); 218.2 (M^-).

C. 2-(2,4-Dimethoxyphenyl)-3-oxobutanenitrile.



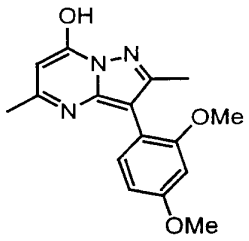
Slurry 4-(2,4-dimethoxyphenyl)-5-methyl-isoxazole (4.4 g) in 1.0 N NaOH (35 mL) and add 35 mL MeOH to dissolve. Heat at 60°C under N_2 for 1 hour, then cool to clear brown solution. Add 1.0 N HCl to acidify to pH 1, then filter the resulting white solid precipitate.

Dissolve solid in EtOAc, dry over Na_2SO_4, filter and concentrate to red oil. Use without further purification. LCMS = 220.2 (MH^+); 218.2 (M^-).

D. 5-Amino-4-(2,4-dimethoxylphenyl)-3-methylpyrazole

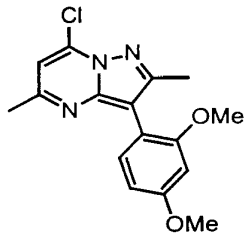
This compound was prepared as described in Example 1F.

E. 7-Hydroxy-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine



This compound was prepared as described in Example 1G.

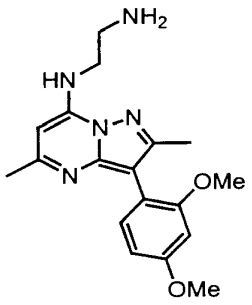
F. 7-Chloro-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine



Slurry 7-hydroxy-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a] pyrimidine in 10 mL $POCl_3$ and reflux at 130°C under N_2. After 2 h, monitoring by TLC (alcohol Rf=0.5, chloride Rf=1.0; EtOAc as eluent), quench the reaction carefully at ambient temperature by diluting with 50 mL CH_2Cl_2 and pouring slowly into non-stirring saturated $NaHCO_3$. Adjust stirring speed to control rate of quenching of residual $POCl_3$ and stir until gas evolution ceases. Separate the layers and extract the aqueous layer with CH_2Cl_2 (2 x 50 mL). Pool the organic

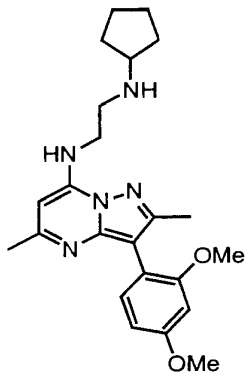
layers and dry over Na_2SO_4. Filter and evaporate to yellow oil, which is used directly without further purification.

G. 7-(2-aminoethylamino)-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a] pyrimidine



Dissolve 7-chloro-2,5-dimethyl-3-(2,4-dimethoxyphenyl)-pyrazolo[1,5-a] pyrimidine in 25 mL CH_3CN, then add excess ethylenediamine (5 mL) and heat to 80°C for 3-6 h under N_2 with attached reflux condenser. (TLC: [10% (2.0M NH_3 in MeOH) / 90% CH_2Cl_2] as eluent). Cool to ambient temperature and evaporate to yellow oil. Partition between CH_2Cl_2 (50 mL) and 1.0 N NaOH (50 mL), and extract aqueous layer 2 x 30 mL CH_2Cl_2. Pool organic layers, dry over Na_2SO_4, filter and evaporate to yellow-white foam. Use without further purification.

H. 7-(2-cyclopentylamino)ethylamino)-3-(2,4-dimethoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine.



This compound was prepared as described in Example 1J.

EXAMPLE 3

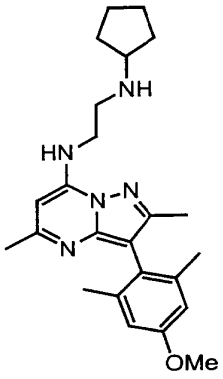
Preparation of 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine

(formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,4-dimethyl-4-methoxyphenyl, R^5 is cyclopentyl)

A. 4-Methoxy-2,6-dimethyl phenyl acetonitrile

Dropwise add a solution of chlorotrimethylsilane (20 mL) in CH_2Cl_2 (40 mL) to a stirred solution cooled to 0°C of 4-methoxy-2,6-dimethyl benzyl alcohol (approx. 74 mmol) in 300 mL CH_2Cl_2. Solution changes color from colorless to yellow and then to purple over the course of the reaction. After 2 h, monitoring by TLC (alcohol Rf=0.25, chloride Rf=0.95; using 20% EtOAc / 80% hexanes as eluent), evaporate down to a yellow oil. Dissolve in dry DMF (50 mL) and cool to 0°C under N_2. Add freshly ground NaCN (7.0 g) portionwise over 5 minute (exothermic) to the stirring reaction, forming a yellow/white slurry. Stir for 5-8 h at 0°C until no starting material remains, as determined by TLC (nitrile Rf=0.5; using 20% EtOAc / 80% hexanes as eluent). Partition the reaction solution between EtOAc (100 mL) and 0.1 N NaOH (300 mL). Dry the EtOAc layer over Na2SO4, filter and evaporate to yellow oil. Chromatograph in 10% EtOAC / 90% hexanes on silica to remove residual chloride and evaporate to 2.1 g yellow solid; clean by TLC. LCMS = 176.5 (MH^+), 174.4 (M^-).

B. 7-(2-(Cyclopentylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine



7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(2,6-dimethyl-4-methoxyphenyl)-pyrazolo[1,5-a] pyrimidine is obtained from 4-methoxy-2,6-dimethyl phenyl acetonitrile using the procedures described in EXAMPLE 1 E, F, G, H, I, and J.

EXAMPLE 4

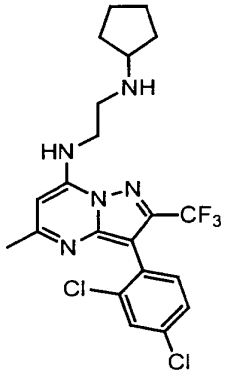
Preparation of 7-(2-(cyclopentylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine

(formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CF_3, R^4 is 2,4-dichlorophenyl, R^5 is cyclopentyl)

A. 2-(2,4-Dichlorophenyl)-4,4,4-trifluoro-3-oxobutanenitrile

Slurry 2,4-dichlorophenylacetonitrile (I) (5.0 g, 26.9 mmol, 186.04 g/mol) in ethyl trifluoroacetate (6.4 mL, 7.6 g, 142.08 g/mol) and add 20 mL anhydrous THF. Portionwise at ambient temperature add NaH (1.88g, 47.1 mmol, 60% in mineral oil) over 5 min. Heat reaction to reflux (90°C bath temperature) overnight. Evaporate to thick red-brown oil and partition between Et_2O (100 mL) and H_2O (60 mL). Separate layers and extract H_2O with Et_2O (2 x 75 mL). Acidify the aqueous layer with 1.0 N HCl to pH 1 (becomes cloudy white suspension) and extract aqueous layer with CH_2Cl_2 (3 x 100 mL). Dry pooled CH_2Cl_2 layers over Na_2SO_4, filter and concentrate to yellow oil (7.5 g, 26.5 mmol). Use without further purification. LCMS = 281.9 (MH^+); 279.8 (M^-)

B. 7-(2-(Cyclopentylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine



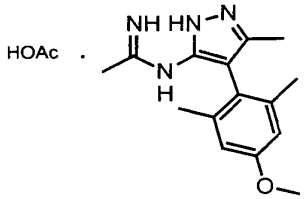
7-(2-(Cyclopentylamino)ethylamino)-2-trifluoromethyl-5-methyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine is obtained from 2-(2,4-dichlorophenyl)-4,4,4-trifluoro-3-oxobutanenitrile using the procedures described in EXAMPLE 1 F, G, H, I, and J.

EXAMPLE 5

Preparation of 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-methoxy-2,6-dimethylphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

(formula I where X is N, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,6-dimethyl-4-methoxyphenyl, R^5 is cyclopentyl)

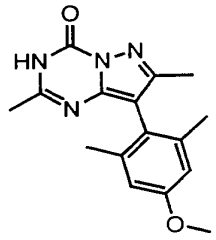
A. (Iminoethyl)[4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazol-5-yl]amine acetate salt.



To a solution of 5-amino-4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazole (1.89 g) in acetonitrile (30 mL) add ethylacetimidate (free base, 1.8 mL) followed by acetic acid (0.47

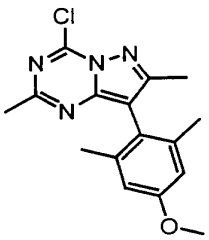
mL). Collect the precipitate that formed upon stirring overnight by filtration. Wash the solid with dry ether and dry to afford 2.61 g of (iminoethyl)[4-(4-methoxy-2,6-dimethylphenyl)-3-methylpyrazol-5-yl]amine acetate salt as a white powder.

B. 2,6-Dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one.



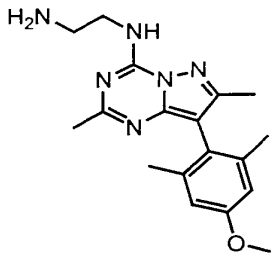
Add sodium pieces (1.81 g) to a flask containing anhydrous ethanol and equipped with a reflux condenser. Allow the mixture to stir until all the sodium is consumed and then add the amidine (2.61 g as the acetate salt) from step A in one portion. Add diethyl carbonate (7.6 mL) and reflux the mixture overnight. Concentrate the mixture under reduced pressure, dissolve the residue in water (75 mL) and adjust the pH to 5 with 3N HCl. Extract the aqueous mixture with EtOAc and wash the extracts with brine, dry over anhydrous sodium sulfate, and concentrate in vacuo to obtain a foam. Stir the residue with hexanes for 20 min and collect the solid by filtration, then wash with hexanes to obtain 2.01 g of 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one as a yellow powder: MS 299 (M+H).

C. 4-Chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine.



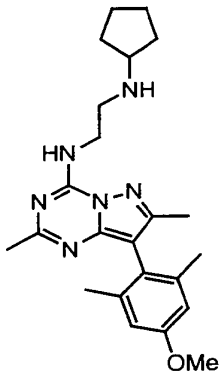
Dissolve 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one from step B (1 g) in $POCl_3$ (50 mL) and add N,N-dimethylaniline (0.55 mL). Reflux the reaction mixture under a dry nitrogen atmosphere for 18h at which time concentrate the mixture under reduced pressure. Dissolve the residue in EtOAc and wash with a saturated aqueous $NaHCO_3$ solution, then with brine. Dry the organic layer over anhydrous sodium sulfate, filter and concentrate under reduced pressure to obtain 4-chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine as a dark oil. MS 317 (M+H).

D. 2,6-Dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine.



Dissolve 4-chloro-2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine in dry toluene (10 mL) to form a stock solution of the chloride (~0.34 M). Add a portion of this solution (8 mL) dropwise into a stirring solution of ethylenediamine (3.6 mL) in acetonitrile (50 mL) which is heated to 60°C. After 3h at 60°C, cool the solution, concentrate under reduced pressure, dilute with 10% NaOH and extract with EtOAc. Wash the combined extracts with brine, dry over anhydrous sodium sulfate and concentrate under reduced pressure to obtain a yellow residue. Triturate the residue with 20% EtOAc/hexanes and collect the resulting solid by filtration to obtain 0.72 g of 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine as a yellow solid: MS 341 (M+H).

E. 7-(2-(Cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-methoxy-2,6-dimethylphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.



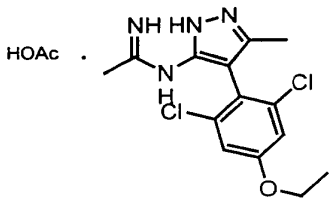
Dissolve 2,6-dimethyl-7-(2,6-dimethyl-4-methoxyphenyl)-4-(2-aminoethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine from step D (0.211 g) in dry dichloroethane (15 mL) and add cyclopentanone (1 equiv). Add acetic acid (35 μL) followed by sodium triacetoxyborohydride (0.184 g) and stir the resulting homogeneous mixture overnight at ambient temperature. Dilute the reaction mixture with 4 volumes of CH_2Cl_2, wash with brine, dry over anhydrous sodium sulfate, and concentrate under reduced pressure to obtain a yellow solid. Purify using preparative thin-layer chromatography [10% MeOH(2N NH_3)/CH_2Cl_2] to obtain 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-methoxy-2,6-dimethylphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

EXAMPLE 6

Preparation of 7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-ethoxy-2,6-dichlorophenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

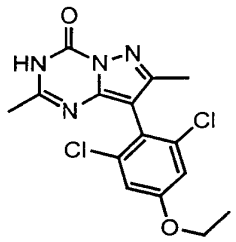
formula I where X is N, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,6-dichloro-4-ethoxyphenyl, R^5 is cyclopentyl.

A. (Iminoethyl)[4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazol-5-yl]amine acetate salt.



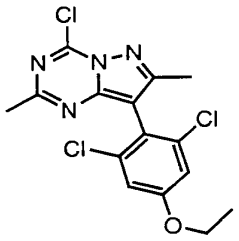
To a solution of 5-amino-4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazole (4.8 g) in acetonitrile (50 mL) add ethylacetimidate (free base, 2.3 mL) followed by acetic acid (0.96 mL). Collect the precipitate that formed upon stirring overnight by filtration. Wash the solid with dry ether and dry to afford 5.02 g of (iminoethyl)[4-(4-ethoxy-2,6-dichlorophenyl)-3-methylpyrazol-5-yl]amine acetate salt as a white powder.

B. 2,6-Dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one.



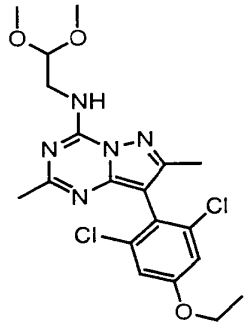
Add sodium pieces (2.98 g) to a flask containing anhydrous ethanol and equipped with a reflux condenser. Allow the mixture to stir until all the sodium is consumed and then add the amidine (5.02 g as the acetate salt) from step A in one portion. Add diethyl carbonate (12.6 mL) and reflux the mixture for four h. Concentrate the mixture under reduced pressure, dissolve the residue in water (75 mL) and adjust the pH to 5 with 3N HCl. Extract the aqueous mixture with EtOAc and wash the extracts with brine, dry over anhydrous sodium sulfate, and concentrate in vacuo to obtain a foam. Stir the residue with hexanes for 20 min and collect the solid by filtration, then wash with hexanes to obtain 4.41 g of 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one as a beige solid: MS 353 (M+H).

C. 4-Chloro-2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine.



Dissolve 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-3H-[1,5-c]-pyrazolo-1,3,5-triazin-4-one from step B (1.05 g) in $POCl_3$ (50 mL) and add 2,6-lutidine (0.45 mL). Reflux the reaction mixture under a dry nitrogen atmosphere for 48h and then concentrate the mixture under reduced pressure. Dissolve the residue in EtOAc and wash with a saturated aqueous $NaHCO_3$ solution, then with brine. Dry the organic layer over anhydrous sodium sulfate, filter and concentrate under reduced pressure to obtain an oil which crystallizes upon standing. Wash the solid with hexanes to remove residual 2,6-lutidine and collect the solid on a sintered glass funnel yielding 4-chloro-2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl) [1,5-a]-pyrazolo-1,3,5-triazine. MS 372 (M+H).

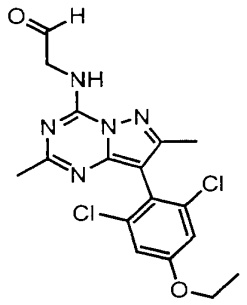
D. 2,6-Dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-4-(2,2-dimethoxyethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine.



Dissolve the product from step C in dry acetonitrile and then add 2.1 equivalents of aminoacetaldehyde dimethyl acetal. Heat the solution to 60°C and stir under a dry nitrogen

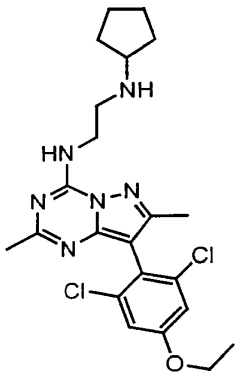
atmosphere for 2-6 h. Remove the solvent under reduced pressure, dilute with 10% NaOH and extract with EtOAc. Wash the combined extracts with brine, dry over anhydrous sodium sulfate and concentrate under reduced pressure to obtain a yellow oil which crystallizes upon standing. The product, 2,6-dimethyl-7-(2,6-dichloro-4-ethoxyphenyl)-4-(2,2-dimethoxyethyl)amino-[1,5-a]-pyrazolo-1,3,5-triazine, is used without further purification. MS (M+H).

E. 2-{[7-(2,6-dichloro-4-ethoxyphenyl)-2,5,6-trimethyl-3-pyrazolino[2,3-a]1,3,5-triazin-4-yl]amino}ethanal.



Dissolve the product obtained from step D in neat trifluoroacetic acid (25mL). After allowing the mixture to stand at ambient temperature for 0.5h, concentrate the mixture under reduced pressure. Add saturated aqueous sodium bicarbonate and stir the resulting heterogeneous mixture for 0.5h. Extract the aqueous solution with EtOAc, wash the EtOAc extracts with brine and then dry over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure yields the aldehyde as an off-white foam. ^{1}H NMR (CDCl3): δ 9.79 (s, 1H, CHO).

F. 7-(2-(Cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-ethoxy-2,6-dichlorophenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.



Dissolve the aldehyde (62 mg, 0.16 mmol) obtained from step E in dry dichloroethane (4 mL). Add 1.1 equivalents of cyclopentylamine followed by 1 equivalent of acetic acid. After the addition of sodium triacetoxyborohydride (1.4 eq), stir the solution at ambient temperature for several h. Dilute the reaction mixture with 4 volumes of CH_2Cl_2 then wash the mixture with brine (1x), dry over anhydrous Na2SO4. Concentrate under reduced pressure. Preparative thin layer chromatography [10% MeOH(2N NH_3)/CH_2Cl_2)] of the oily residue yields7-(2-(cyclopentylamino)ethylamino)-2,5-dimethyl-3-(4-ethoxy-2,6-dichlorophenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

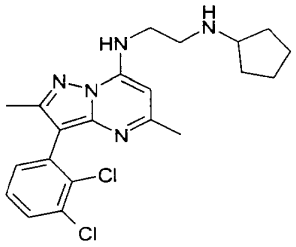
The preparation of the compounds of the present invention by the above-mentioned methods is illustrated further by the following examples, delineated in the TABLE which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. Commonly used abbreviations are: Ph is phenyl, Me is methyl, Et is ethyl, Pr is n-propyl, iPr is isopropyl, cPr is cyclopropyl, Bu is butyl, iBu is isobutyl (CH_2-$CHMe_2$), tBu is tert-butyl, cBu is cyclobutyl, Pent is n-pentyl, cPent is cyclopentyl, cHex is cyclohexyl, Py is pyridyl, Bn is benzyl (CH_2Ph), Ac is acetyl (CH_3-(C=O)), tBOC is tert-butyloxycarbonyl (tBuO-(C=O)). EX means example.

By way of further exemplification, details of the preparation used in Example 14 which is included in the Table are as follows:

EXAMPLE 14

Preparation of N-cyclopentyl-N'-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine hydrochloride salt

formula I where X is CH, R^1 is CH_3, R^2 is H, A is CH_2, B is CH_2, R^3 is CH_3, R^4 is 2,3-dichloro-4-ethoxyphenyl, R^5 is cyclopentyl, R^6 is H.



A. 7-Chloro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

2,5-Dimethyl-4H-pyrazolo[1,5-a]pyrimidin-7-one (3.5 g, 21 mmol) in phosphorus oxychloride (20 mL) was stirred at reflux. After 3 hours the dark purple reaction was cooled and then extracted from ice water with ethyl acetate. The combined organic layers were washed with water and saturated aqueous sodium bicarbonate, dried (Na_2SO_4) and then concentrated under reduced pressure to give the title compound (3.0 g, 77%) as a brown solid: +APcI MS $(M+1)^+$ 182; ^1H NMR ($CDCl_3$) δ: 6.74 (s, 1H), 6.42 (s, 1H), 2.55 (s, 3H), 2.53 (s, 3H).

B. N-(2,5-Dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine

To a stirred solution of 7-chloro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (3.0 g, 16.5 mmol) in ethanol (60 mL) was added ethylene diamine (4 mL, 60 mmol). After refluxing 18 hours the reaction was cooled, poured into saturated aqueous sodium bicarbonate, and then washed with ethyl acetate. The aqueous layer was then extracted with 3:7 isopropyl alcohol/chloroform, the combined extracts were dried (Na_2SO_4) and then concentrated under reduced pressure to give the title compound as an amorphous brown solid (3.2 g, 94%): +APcI MS $(M+1)^+$ 206; ^1H NMR (methanol-d_4) δ: 6.05 (s, 1H), 6.00 (s, 1H), 3.45 (m, 2H), 2.91 (m, 2H).

C. N-Cyclopentyl-N'-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine

To a stirred solution of N-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine (3.2 g, 16 mmol) and cyclopentanone (2.7 mL, 30 mmol) in methanol (30 mL)/acetic acid (3 mL) was added sodium cyanoborohydride (0.94 g, 15 mmol), portionwise. After stirring 1 hour the reaction was concentrated under reduced pressure and then extracted from saturated aqueous sodium bicarbonate with ethyl acetate. The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure to give the crude product as a brown oil (5.6 g): +APcI MS $(M+1)^+$ 274; ^1H NMR ($CDCl_3$) δ: 6.11 (s, 1H), 6.76 (s, 1H), 3.21 (t, 2H), 3.21 (m, 1H), 3.04 (t, 1H), 2.42 (s, 3H), 2.40 (s, 3H).

D. Cyclopentyl-[2-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester

To a stirred solution of the crude N-cyclopentyl-N'-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-ethane-1,2-diamine (5.6 g) in methylene chloride (24 mL)/methanol (2 mL) was added di-tert-butyl dicarbonate (5.1 g, 23 mmol) and then 4- dimethylaminopyridine (0.6 g, 4.9 mmol). After stirring 5 hours the reaction was concentrated under reduced pressure and then chromatographed (1:1 ethyl acetate/hexanes) to afford the title compound as an orange glass (2.3 g, 39% from B)): +APcI MS $(M+1)^+$ 374; ^1H NMR ($CDCl_3$) δ: 6.16 (s, 1H), 5.78 (s, 1H), 4.25-4.15 (br s, 1H), 3.47 (m, 4H), 2.47 (s, 3H), 2.41 (s, 3H), 1.51 (s, 9H).

E. Cyclopentyl-[2-(3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester

To a 0 °C stirred solution of cyclopentyl-[2-(2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester (89 mg, 0.24 mmol) in chloroform (5 mL) was added N-iodosuccinimide (54 mg, 0.24 mmol). After stirring 30 minutes the reaction was extracted from saturated aqueous sodium thiosulfate with chloroform. The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure to give the product as a slightly yellowed glass

(102 mg, 85%): +APcI MS $(M+1)^+$ 500; ^{1}H NMR ($CDCl_3$) δ: 5.82 (s, 1H), 4.25-4.10 (br s, 1H), 3.46 (s, 4H), 2.51 (s, 3H), 2.41 (s, 3H), 1.50 (s, 9H).

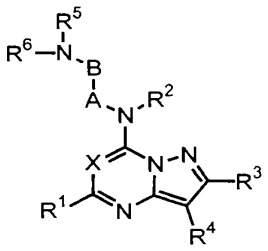
F. Cyclopentyl-{2-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-carbamic acid tert-butyl ester

A suspension of cyclopentyl-[2-(3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino)-ethyl]-carbamic acid tert-butyl ester (38 mg, 0.076 mmol) and 2,3-dichlorobenzeneboronic acid in toluene (0.5 mL)/ethanol (0.5 mL)/2 M aqueous sodium carbonate (0.22 mL) was degassed (3X) by alternately pulling a vacuum followed by repressurization with nitrogen. Tetrakis(triphenylphosphine)palladium (10 mg, 0.009 mmol) was added, and the mixture was degassed (3X) again. The mixture was stirred for 2.5 hours at 100 °C, concentrated under reduced pressure, and then chromatographed (4:1 hexanes/ethyl acetate) to give the product as colorless oil (24 mg, 60%): +APcI MS $(M+1)^+$ 518; ^{1}H NMR ($CDCl_3$) δ: 7.42 (dd, 1H), 7.30 (dd, 1H), 7.22 (t, 1H), 5.84 (s, 1H), 4.25-4.10 (br s, 1H), 3.49 (s, 4H), 2.44 (s, 3H), 2.32 (s, 3H), 1.52 (s, 9H).

G. N-Cyclopentyl-N'-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine hydrochloride salt

The cyclopentyl-{2-[3-(2,3-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-carbamic acid tert-butyl ester (21mg, 0.040 mmol) was stirred for 1 hour in 2:1 ethanol/concentrated aqueous hydrochloric acid (1.5 mL), concentrated under reduced pressure, and then concentrated 2 additional times from ethanol to give the title compound (17 mg, 94%): +APcI MS $(M+1)^+$ 418; ^{1}H NMR (methanol-d_4) δ: 7.69 (d, 1H), 7.50-7.40 (m, 2H), 6.78 (s, 1H), 4.06 (br s, 2H), 3.63 (br m, 1H), 3.42 (br s, 2H), 2.60 (s, 3H), 2.34 (s, 3H).

Table of Examples



EX	X	R^1	R^2	R^3	R^4	A-B-N[R^6]-R^5	MW
7.	CH	Me	H	Me	2-Cl-4-F-Ph	(CH2)2-NH-cHex	415.93
8.	CH	Me	H	Me	2-Cl-4-F-Ph	(CH2)2-NH-cPent	401.92
9.	CH	Me	H	Me	2-Cl-4-OEt-Ph	(CH2)2-NH-cPent	427.98
10.	CH	Me	H	Me	2-Cl-6-F-Ph	(CH2)2-NH-cPent	401.91
11.	CH	Me	H	Me	2-Cl-Ph	(CH2)2-NH-cPent	383.93
12.	CH	Me	H	Me	2-F-4-Br-Ph	(CH2)2-NH-cPent	482.83
13.	CH	Me	H	Me	2-F-Ph	(CH2)2-NH-cPent	367.47
14.	CH	Me	H	Me	2,3-diCl-Ph	(CH2)2-NH-cPent	418.37
15.	CH	Me	H	Me	2,4-diCl-6-OMe-Ph	(CH2)2-NH-cPent	448.4
16.	CH	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-cBu	404.24
17.	CH	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-CH2-cPr	404.34
18.	CH	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-cHex	432.39
19.	N	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-cHex	433.4
20.	CH	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-cPent	418.36
21.	N	Me	H	Me	2,4-diCl-Ph	(CH2)2-NH-cPent	419.4
22.	CH	Me	H	Me	2,4-diF-6-OEt-Ph	(CH2)2-NH-cPent	465.98
23.	CH	Me	H	Me	2,4-diF-Ph	(CH2)2-NH-cHex	399.48
24.	CH	Me	H	Me	2,4-diF-Ph	(CH2)2-NH-cPent	385.45
25.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH2)2-NH-cPent	443.98
26.	CH	Me	H	Me	2,4-diOMe-6Cl-Ph	(CH2)2-NH2	375.9
27.	CH	Me	H	Me	2,4-diOMe-Ph	(CH2)2-NH-cHex	423.55
28.	CH	Me	H	Me	2,4,6-triF-Ph	(CH2)2-NH-cPent	439.91
29.	CH	Me	H	Me	2,4,6-triMe-Ph	CH2-(2-Me-piperidin-6-yl)	391.6
30.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cBu	377.53
31.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-CH2-cPr	377.53

32.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cHex	405.59
33.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cHex	419.61
34.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent	391.55
35.	CH	Me	H	CF3	2,4,6-triMe-Ph	(CH2)2-NH-cPent	445.52
36.	N	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent	392.5
37.	CH	Et	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-cPent	405.59
38.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-iBu	379.55
39.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-iPr	365.52
40.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)2-NH-tBu	379.54
41.	CH	Me	H	Me	2,4,6-triMe-Ph	(CH2)3-NH-cPent	405.59
42.	CH	Me	H	Me	2,5-diCl-Ph	(CH2)2-NH-cPent	418.37
43.	CH	Me	H	Me	2,5-diF-Ph	(CH2)2-NH-cHex	385.46
44.	N	Me	H	Me	2,5-diMe-4-OMe-Ph	(CH2)2-NH-cHex	422.6
45.	CH	Me	H	Me	2,5-diMe-4-OMe-Ph	(CH2)2-NH-cHex	421.59
46.	N	Me	H	Me	2,5-diMe-4-OMe-Ph	(CH2)2-NH-cPent	408.5
47.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH2)2-NH-(CH2)2-NH2	394.31
48.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH2)2-NH-CH2-CMe2-NH2	422.36
49.	N	Me	H	Me	2,6-diCl-4-OEt-Ph	(CH2)2-NH2	395.3
50.	CH	Me	H	Me	2,6-diCl-4-OEt-Ph	CH2-CHMe-NH2	408.33
51.	CH	Me	H	Me	2,6-diCl-4-OH-Ph	(CH2)2-NH-cPent	434.37
52.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	4-NH2-cHex	434.37
53.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	4-NH2-cHex	434.37
54.	CH	iPr	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-CHEt-NH2	450.4
55.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-(2-Me-piperidin-6-yl)	448.4
56.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-N(CH2-cPr)2	488.46
57.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(3-NH2-cHex)	434.37
58.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(cis-2-NH2-cHex)	434.37
59.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-(trans-2-NH2-cHex)	434.37
60.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CH2-cPr	434.37
61.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-CHMe-Et	436.39
62.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-cPent	448.4
63.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH-Et	408.33
64.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH2	380.28
65.	CH	iPr	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH2	408.33
66.	CH	tBu	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH2	422.4
67.	CH	nPr	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH2	408.3
68.	CH	CF3	H	Me	2,6-diCl-4-OMe-Ph	(CH2)2-NH2	434.3

69.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)3-NH-Et	422.36
70.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	(CH2)3-NH2	394.31
71.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-(piperidin-2-yl)	434.3
72.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-CHMe-NH2	394.3
73.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	CH2-CHMe-NH2	408.33
74.	CH	iPr	H	Me	2,6-diCl-4-OMe-Ph	CH2-CHMe-NH2	422.36
75.	CH	nPr	H	Me	2,6-diCl-4-OMe-Ph	CH2-CHMe-NH2	422.36
76.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-CMe2-CH2-NH2	422.36
77.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-CMe2-CH2-NH2	477.44
78.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CH2-CMe2-NH2	408.33
79.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	CHMe-CHMe-NH2	408.33
80.	CH	Et	H	Me	2,6-diCl-4-OMe-Ph	CHMe-CHMe-NH2	422.4
81.	CH	Me	H	Me	2,6-diCl-4-OMe-Ph	pyrrolidin-3-yl	406.3
82.	CH	Me	H	Me	2,6-diCl-Ph	(CH2)2-NH-cPent	418.37
83.	N	Me	H	Me	2,6-diCl-Ph	(CH2)2-NH-cPent	419.4
84.	CH	Me	H	Me	2,6-diCl-Ph	(CH2)2-NH-Et	378.30
85.	CH	Me	H	Me	2,6-diF-4-OEt-Ph	(CH2)2-NH-cPent	465.98
86.	CH	Me	H	Me	2,6-diF-Ph	(CH2)2-NH-cPent	385.46
87.	CH	Me	H	Me	2,6-diMe-4-OCF3-Ph	(CH2)2-NH-cPent	461.52
88.	N	Me	H	Me	2,6-diMe-4-OMe-Ph	(CH2)2-NH2	340.4
89.	CH	Me	H	Me	2,6-diMe-4-tBu-Ph	(CH2)2-NH-cPent	433.65
90.	N	Me	H	Me	2Cl-4F-Ph	(CH2)2-NH-cHex	416.9
91.	N	Me	H	Me	2Cl-4F-Ph	(CH2)2-NH-cPent	402.9

EXAMPLE 92

Cyclopentyl-{1-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-piperidin-3-yl}-amine (MW 488.5)

EXAMPLE 93

7-piperazino-2,5-dimethyl-3-(2,4-dichlorophenyl)-pyrazolo[1,5-a] pyrimidine (MW 376.28)

EXAMPLE 94

Characterization of NPY receptor interactions and in vivo function

A. Assay for Human NPY_1 Receptor Binding Activity: Compounds are assayed for activity using the following method: A cDNA encoding human NPY1 (SEQ ID NO:1) is ligated in the appropriate orientation for expression into the commercial expression vector pBacPAK9 (Clontech, Palo Alto, CA) for expression in SF9 cells. Each Baculoviral expression vector is co-transfected along with BACULOGOLD DNA (BD PharMingen, San Diego, CA) into S*f*9 cells. The S*f*9 cell culture supernatant is harvested three days post-transfection. The recombinant virus-containing supernatant is serially diluted in Hink's TNM-FH insect medium (JRH Biosciences, Kansas City) supplemented Grace's salts and with 4.1mM L-Gln, 3.3 g/L LAH, 3.3 g/L ultrafiltered yeastolate and 10% heat-inactivated fetal bovine serum (hereinafter "insect medium") and plaque assayed for recombinant plaques. After four days, recombinant plaques are selected and harvested into 1 ml of insect medium for amplification. Each 1 ml volume of recombinant baculovirus (at passage 0) is used to infect a separate T25 flask containing 2×10^6 S*f*9 cells in 5 mls of insect medium. After five days of incubation at 27°C, supernatant medium is harvested from each of the T25 infections for use as passage 1 inoculum. Recombinant baculoviral clones are then subjected to a second round of amplification, using 1 ml of passage 1 stock to infect 1×10^8 cells in 100 ml of insect medium divided into 2 T175 flasks. Forty-eight hours post infection, passage 2 medium is harvested from each 100ml prep and plaque assayed for titer. The cell pellets from the second round of amplification are assayed for affinity binding of radiolabeled ligand (see below) to verify recombinant receptor expression. A third round of amplification is then initiated using an M.O.I. of 0.1 to infect a liter of S*f*9 cells. Forty hours post-infection the supernatant medium is harvested to yield passage 3 baculoviral stock and the cell pellet assayed for affinity binding. Titer of the passage 3 baculoviral stock is determined by plaque assay and an M.O.I. and Incubation Time Course experiment is carried out to determine conditions for optimal receptor expression.

Log-phase S*f*9 cells are infected with stocks of recombinant baculovirus encoding the proteins of interest (e.g., human NPY1 and three g-proteins), followed by culturing in insect medium at 27°C. 72 hours post-infection, a sample of cell suspension is analyzed for viability by

trypan blue dye exclusion, and the remaining *Sf*9 cells are harvested via centrifugation (3000 rpm/ 10 min/ 4°C).

Preparation of purified membranes: *Sf*9 cell pellets are resuspended in homogenization buffer (10 mM HEPES, 250 mM sucrose, 0.5 □g/ml leupeptin, 2 □g/ml Aprotinin, 200 □M PMSF, and 2.5 mM EDTA, pH 7.4) and homogenized using a POLYTRON homogenizer (setting 5 for 30 seconds). The homogenate is centrifuged (536 x g/ 10 min/ 4°C) to pellet the nuclei. The supernatant containing isolated membranes is decanted to a clean centrifuge tube, centrifuged (48,000 X g/ 30 min, 4°C) and resuspended in 30 ml, or preferably 20 ml of homogenization buffer. This centrifugation and resuspension step is repeated twice. The final pellet is resuspended in ice cold Dulbecco's PBS containing 5 mM EDTA and stored in frozen aliquots until needed at -80°C. The protein concentration of the resulting membrane preparation is measured using the Bradford protein assay (Bio-Rad Laboratories, Hercules, CA). By this measure, a 1-liter culture of cells typically yields 50-100 mg of total membrane protein.

CO-infection for GTPγ^{35}S binding assay: Four baculoviral expression vector stocks are used to infect a culture of *Sf*9 cells with an MOI of 1:1:1:1. These four consisted of one vector encoding the human NPY1 receptor and a different commercially obtained baculoviral expression vector stock encoding each of the three subunits of a heterotrimeric G-protein, in particular, the G-protein-encoding virus stocks are obtained from BIOSIGNAL Inc., Montreal, and are **1)** a Gα G-protein subunit-encoding virus stock (either the rat $G\alpha_{i2}$ G-protein-encoding virus stock BIOSIGNAL #V5J008 or the rat $G\alpha_O$ G-protein-encoding virus stock BIOSIGNAL #V5H010), **2)** a bovine β1 G-protein-encoding virus stock (BIOSIGNAL #V5H012), and **3)** a human γ2 G-protein-encoding virus stock (BIOSIGNAL #V6B003). Agonist-stimulated GTPγ^{35}S binding on purified membranes is assessed using hNPY 1-36 (American Peptide Co., Sunnyvale, CA) as agonist in order to ascertain functional activity as measured by GTPγ^{35}S binding.

B. GTPγ^{35}S binding assay: Purified *Sf*9 cell membranes are resuspended by Dounce homogenization (tight pestle) in GTPγ^{35}S binding assay buffer (50 mM Tris pH 7.0, 120 mM NaCl, 2 mM MgCl2, 2 mM EGTA, 0.1% BSA, 0.1 mM bacitracin, 100KIU/mL Aprotinin, 5 μM GDP) and added to reaction tubes at a concentration of 30 μg/reaction tube. After adding increasing doses of the agonist hNPY 1-36 (American Peptide Co., Sunnyvale, CA), reactions

are initiated by the addition of 100 pM GTPγ^{35}S. Following a 30-minute incubation at ambient temperature, the reactions are terminated by vacuum filtration over GF/C filters (pre-soaked in wash buffer, 0.1% BSA) followed by washing with ice-cold wash buffer (50 mM Tris pH 7.0, 120mM NaCl).

Bound GTPγ^{35}S is determined by liquid scintillation spectrometry of the washed filters. Non-specific binding is determined using 10 mM GTPγS. Data are generally expressed as % maximal response and are derived by determining the maximal agonist stimulated % above basal stimulation. Computer analysis may be conveniently used to calculate estimated EC_{50}, IC_{50} and K_i values from GTPγ^{35}S binding experiment data, e.g., using SigmaPlot software. The binding affinity for the preferred compounds of the invention, expressed as K_i values, ranges from about 0.1 nanomolar to about 5 micromolar. Particularly preferred compounds yield a K_i value of less than 100 nanomolar, most preferably less than 10 nanomolar .

Assay for affinity binding of radiolabeled ligand: Purified membranes are washed with PBS and re-suspended by gentle pipetting in binding buffer (50 mM Tris(HCl), 5 mM KCl, 120 mM NaCl, 2 mM CaCl2, 1 mM MgCl2, 0.1% bovine serum albumin (BSA), pH 7.4). Membranes (5μg) are added to siliconized (Sigmacote, Sigma) polypropylene tubes in addition to 0.050 nM [125I]NPY (porcine, New England Nuclear Corp., Boston, MA) for competition analysis or 0.010-0.500 nM [125I]NPY (porcine) for saturation analysis. For evaluation of guanine nucleotide effects on receptor affinity, GTP is added at a final concentration of 100 μM. Cold displacers are added at concentrations ranging from 10-12 M to 10-6 M to yield a final volume of 0.250 mL. Nonspecific binding is determined in the presence of 1 μM NPY (human, American Peptide Co., Sunnyvale, CA) and accounts for less than 10% of total binding. Following a 2-hour incubation at ambient temperature, the reaction is terminated by rapid vacuum filtration. Samples are filtered over presoaked GF/C Whatman filters (1.0% polyethyleneimine for 2 hours) and rinsed 2 times with 5 mL cold binding buffer lacking BSA. Remaining bound radioactivity is measured by gamma counting. To estimate the Bmax, Kd and Ki, the results of binding experiments are analyzed using SigmaPlot software (SPSS Science, Chicago, IL). The binding affinity for the compounds of the invention, expressed as a Ki value, ranges from about 0.1 nanomolar to about 10 micromolar. The most preferred compounds of the

invention have a Ki of less than 100 nanomolar and a binding selectivity of >100-fold relative to other G-protein coupled receptors, including NPY_5 and $CRF1_1$ receptors.

C. *In vivo* analysis - Food Deprivation

Subjects. Experimentally naive and experienced male Sprague-Dawley rats (Sasco, St. Louis, MO) weighing 210-300g at the beginning of the experiment are used. Animals are triple-housed in stainless steel hanging cages in a temperature (22 C ± 2) and humidity (40-70% RH) controlled animal facility with a 12:12 hour light-dark cycle. Food (Standard Rat Chow, PMI Feeds Inc., #5012) and water are available ad libitum.

Apparatus. Consumption data is collected while the animals are housed in Nalgene Metabolic cages (Model #650-0100). Each cage is comprised of subassemblies made of clear polymethlypentene (PMP), polycarbonate (PC), or stainless steel (SS). All parts disassemble for quick and accurate data collection and for cleaning. The entire cylinder-shaped plastic and SS cage rests on a SS stand and houses one animal.

The animal is contained in the round Upper Chamber (PC) assembly (12cm high and 20cm in diameter) and rests on a SS floor. Two subassemblies are attached to the Upper Chamber. The first assembly consists of a SS feeding chamber (10cm long, 5cm high and 5cm wide) with a PC feeding drawer attached to the bottom. The feeding drawer has two compartments: a food storage compartment with the capacity for approximately 50g of pulverized rat chow, and a food spillage compartment. The animal is allowed access to the pulverized chow by an opening in the SS floor of the feeding chamber. The floor of the feeding chamber does not allow access to the food dropped into the spillage compartment.
The second assembly includes a water bottle support, a PC water bottle (100ml capacity) and a graduated water spillage collection tube. The water bottle support funnels any spilled water into the water spillage collection tube.

The lower chamber consists of a PMP separating cone, PMP collection funnel, PMP fluid (urine) collection tube, and a PMP solid (feces) collection tube. The separating cone is attached to the

top of the collection funnel, which in turn is attached to the bottom of the Upper Chamber. The urine runs off the separating cone onto the walls of the collection funnel and into the urine collection tube. The separating cone also separates the feces and funnels it into the feces collection tube.

Food consumption, water consumption, and body weight may be measured with an Ohaus Portable Advanced scale (±0.1g accuracy).

Procedure. Prior to the day of testing, animals are habituated to the testing apparatus by placing each animal in a Metabolic cage for 1 hour. On the day of the experiment, animals that have been food deprived the previous night are weighed and assigned to treatment groups. Assignments are made using a quasi-random method utilizing the body weights to assure that the treatment groups had similar average body weight. Animals are then administered either vehicle (0.5% methyl cellulose) or drug (a compound of the invention). At that time, the feeding drawer is filled with pulverized chow, the filled water bottle, and the empty urine and feces collection tubes are weighed. Two hours after drug treatment, each animal is weighed and placed in a Metabolic Cage. Following a one-hour test session, animals are removed and body weight obtained. The food and water containers are then weighed and the food and water consumption data recorded.

Drugs. Drug suspended in vehicle, or vehicle alone as a control, is administered orally (PO) using a gavage tube connected to a 3 or 5ml syringe at a volume of 10ml/kg. Drug is made into a homogenous suspension by stirring and ultrasonicating for at least 1 hour prior to dosing.

Statistical Analyses. The means and standard errors of the mean (SEM) for food consumption, water consumption, and body weight change are obtained. One-way analysis of variance using Systat (5.2.1) is used to test for group differences. A significant effect is defined as having a p value of $<.05$.

The following parameters are defined: Body weight change is the difference between the body weight of the animal immediately prior to placement in the metabolic cage and its body weight at

the end of the one hour test session. Food consumption is the difference in the weight of the food drawer prior to testing and the weight following the 1-hour test session. Water consumption is the difference in the weight of the water bottle prior to testing and the weight following the 1-hour test session. Preferred compounds of the invention reduce food intake and body weight gain, preferably to a statistically significant degree as determined by standard parametric analysis such as a student's T-test.

Example 95

Assay for CRF Receptor Binding Activity

As discussed above, the following assay is defined herein as a standard in vitro CRF receptor binding assay. The assay may be used to demonstrate CRF1 receptor-binding activity. The CRF receptor binding is performed using a modified version of the assay described by Grigoriadis and De Souza (*Methods in Neurosciences,* Vol. 5, 1991). IMR-32 human neuroblastoma cells, a cell-line that naturally expresses the CRF1 receptor, are grown to confluency in DMEM containing FBS.

To prepare receptor-containing membranes, cells are homogenized in wash buffer (50 mM Tris HCl, 10 mM $MgCl_2$, 2 mM EGTA, pH 7.4) and centrifuged at 48,000g for 10 min at 4°C. The pellet is re-suspended in wash buffer and the homogenization and centrifugation steps are performed two additional times.

Membrane pellets containing CRF receptors are re-suspended in 50 mM Tris buffer pH 7.7 containing 10 mM $MgCl_2$ and 2 mM EDTA and centrifuged for 10 min at 48000 x g. Membranes are washed again and brought to a final concentration of 1500 mg/ml in binding buffer (Tris buffer above with 0.1 % BSA, 15 mM bacitracin and 0.01 mg/ml aprotinin.). For the binding assay, 100 ml of the membrane preparation are added to 96 well microtube plates containing 100 ml of ^{125}I-CRF (SA 2200 Ci/mmol, final concentration of 100 pM) and 50 ml of test compound. Binding is carried out at ambient temperature for 2 h. Plates are then harvested on a Brandel 96 well cell harvester and filters are counted for gamma emissions on a Wallac 1205 Betaplate liquid scintillation counter. Non specific binding is defined by 1 mM cold CRF. IC_{50} values are calculated with the non-linear curve fitting program RS/1 (BBN Software Products Corp., Cambridge, MA). The binding affinity for a compound of Formula I expressed as an IC_{50} value generally ranges from about 0.5 nanomolar to about 10 micromolar.

Example 96

Preparation of radiolabeled probe compounds of the invention

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

Example 97

Preparation of radiolabeled probe compounds of the invention

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

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

Example 98

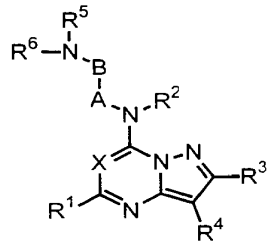
Receptor autoradiography

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

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

WHAT IS CLAIMED IS:

1. A compound of the formula



I

or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

X is N or CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^7, R^7 cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

2. A compound according to Claim 1, wherein X is N.

3. A compound according to Claim 1, wherein

X is N; and

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

4. A compound according to Claim 1, wherein

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl; and

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl.

5. A compound according to Claim 1, wherein

X is N;

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^5 is H.

6. A compound according to Claim 1, wherein;

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl;

R^4 is phenyl, mono-, di-, or tri-substituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and

R^7, R^8, and R^9 are as defined in Claim 1.

7. A compound according to Claim 1, wherein:

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is H; and

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

8. A compound according to Claim 1, wherein:

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

9. A compound according to Claim 1, wherein X is CH.

10. A compound according to Claim 1, wherein

X is CH; and

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

11. A compound according to Claim 1, wherein

X is CH;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl; and

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl.

12. A compound according to Claim 1, wherein

X is N;

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^5 is H.

13. A compound according to Claim 1, wherein;

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl;

R^4 is phenyl, mono-, di-, or tri-substituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and

R^7, R^8, and R^9 are as defined in Claim 1.

14. A compound according to Claim 1, wherein:

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is H; and

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

15. A compound according to Claim 1, wherein:

X is N;

R^1 is C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl; and

R^4 is phenyl, mono-, di-, or trisubstituted with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), wherein at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted; and

R^6 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl.

16. A compound according to Claim 1 wherein the compound exhibits a 20-fold greater affinity for the NPY1 receptor in a assay of NPY1 receptor binding than for the CRF1 receptor in an assay of CRF1 receptor binding.

17. A compound according to Claim 1 wherein the compound exhibits a 100-fold greater affinity for the NPY1 receptor in a assay of NPY1 receptor binding than for the CRF1 receptor in an assay of CRF1 receptor binding.

18. A method for treating eating disorders and cardiovascular disorders comprising administering to a patient suffering from an eating disorder or cardiovascular disorder a compound according to Claim 1.

19. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

20. A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 19 in a container and comprising instructions for using the composition to treat a patient suffering from an eating disorder or hypertension.

21. A method for localizing NPY receptors in tissue section samples comprising: contacting with a sample of tissue a detectably-labeled compound of Claim 1 under conditions that permit binding of the compound to the sample of tissue; washing the tissue sample to remove unbound compound; and detecting the bound compound.

22. The method of Claim 21, wherein the compound is radiolabeled.

23. A method of inhibiting the binding of NPY to the NPY1 receptor, which method comprises contacting, in the presence of NPY, a solution comprising a compound of Claim 1 with cells expressing the NPY1 receptor, wherein the compound is present in the solution at a

concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

24. A method for altering the signal-transducing activity of a cell surface NPY1 receptor, said method comprising contacting cells expressing such a receptor with a solution comprising a compound according to Claim 1, wherein the compound is present in the solution at a concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

25. A compound according to any one of Claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 1 micromolar or less.

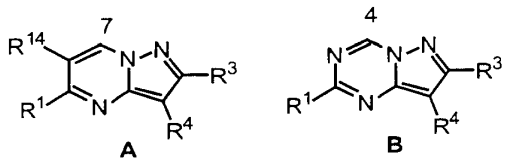
26. A compound according to any one of Claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 100 nanomolar or less.

27. A compound according to any one of Claim 1 wherein in an assay of NPY binding the compound exhibits an K_i of 100 nanomolar 10 nanomolar or less.

28. A method for treating obesity or bulimia nervosa which comprises administering an effective amount of a compound according to Claim 1 to a patient in need thereof.

29. A method for treating hypertension which comprises administering an effective amount of a compound according to Claim 1 to a patient in need thereof.

30. A method of converting a heterocyclic cores **A** and or a heterocyclic core **B**



to a compound that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding,

wherein

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN;

by substituted the 7-position of the heterocyclic core **A** or the 4-position of the heterocyclic core **B** with a diamine group –$N[R^2]$-A-B-$N[R^6]$-R^5

wherein:

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,

or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6

alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^7, R^7 cannot be H;

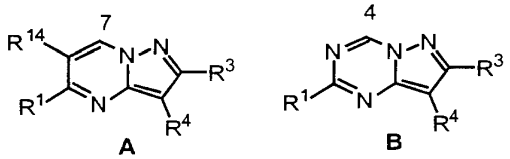
R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle; and

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H.

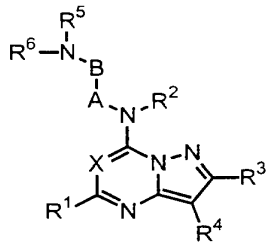
31. A method of converting a heterocyclic cores **A** and or a heterocyclic core **B**



to a compound that exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

exhibits a 20-fold greater affinity for the NPY1 receptor in a assay of NPY1 receptor binding than for the CRF1 receptor in an assay of CRF1 receptor binding.

32. A compound of the formula



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or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

X is N or CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^2 is H,

C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with

R^7,

C_3-C_{10} cycloalkyl, or

(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or

R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-

C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1 – C_6, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7, aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), with the proviso that at least one of the positions ortho or para to the point of attachment of the aryl or heteroaryl ring to the pyrazole is substituted;

R^5 is H;

R^6 and C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that for SO_2R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

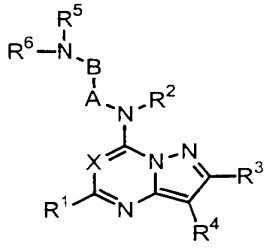
R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

33. A compound of the formula



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or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound exhibits a K_i of 5 micromolar or less in an assay of NPY receptor binding, and

X is N or CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^2 is H,
C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with
R^7,
C_3-C_{10} cycloalkyl, or
(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or
R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7,

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, halogen, C_1-C_6 haloalkyl, CN, alkylsulfonyl, OR^7, NR^8R^9, $CONR^8R^9$, $COOR^7$, $SO_2NR^8R^9$, COR^7, SO_2R^7.

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents

independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

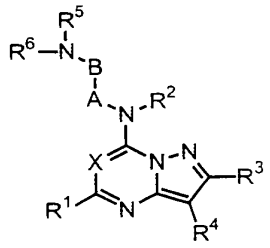
R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

34. A compound of formula



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or a pharmaceutically acceptable salt, hydrate, or prodrug wherein:

X is N or CR^{14};

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^2 is H,
C_1-C_6 alkyl which optionally forms a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle with A or B, each of which is optionally substituted with
R^7,
C_3-C_{10} cycloalkyl, or
(C_3-C_{10} cycloalkyl) C_1-C_6 alkyl; or
R^2 and R^6 jointly form with the 2 nitrogen atoms to which they are bound a C_2-C_5 aminoheterocycle optionally substituted with R^7;

A is $(CH_2)_m$ where m is 1,2 or 3 and is optionally mono- or di-substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or
A and B jointly form a C_3-C_6 carbocycle, which is optionally substituted at each carbon atom with R^7, or

A and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7;

B is $(CH_2)_n$ where n is 0, 1, 2, or 3 and is optionally substituted at each carbon atom with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halogen, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7; C_1-C_6 cyanoalkyl, NR^8R^9, or C_1-C_6 alkyl-NR^8R^9, or

B and R^2 jointly form a C_3-C_6 aminocarbocycle , which is optionally substituted at each carbon atom with R^7, or

B and R^6 jointly form a C_3-C_6 aminocarbocycle, which is optionally substituted at each carbon atom with R^7;

R^3 is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, halo, C_1-C_6 haloalkyl, OR^7, C_1-C_6 alkyl-OR^7, C_1-C_6 cyanoalkyl, NR^8R^9, and C_1-C_6 alkyl-NR^8R^9;

R^4 is selected from aryl or heteroaryl, each substituted with aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), heterocycloalkyl, cyclopentenyl, cyclohexenyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl , trifluoromethylsulfonyl, C_1-C_6 alkyl-NR^8R^9, C_1-C_6 alkyl-CN , C_1-C_6 alkyl-$CONR^8R^9$, (C_1-C_4)alkyl-OR^7, C_1-C_6 alkyl-$COOR^7$and optionally substituted with 1 to 4 substituents independently selected at each occurrence from C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl-$CONR^8R^9$, $COOR^7$, C_1-C_6 alkyl-$COOR^7$, CN, C_1-C_6 alkyl-CN, $SO_2NR^8R^9$, SO_2R^7.

R^5 and R^6 are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^7 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl,

or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl each of which is optionally substituted with 1 to 5 substituents independently selected at each occurrence from halogen, C_1-C_6 haloalkyl, OR^{13}, NR^8R^9, C_1-C_6 alkyl-OR^{13}, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, $COOR^{13}$, CN, $SO_2NR^8R^9$, SO_2R^{13}, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H;

R^8 and R^9 are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_3-C_{10} cycloalkenyl, C_2-C_6 alkynyl, heterocycloalkyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl, or R^8 and R^9, taken together, can form a C_3-C_6 aminocarbocycle or a C_2-C_5 aminoheterocycle each optionally substituted at each occurrence with C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_1-C_3 haloalkyl, or heterocycloalkyl, C_1-C_8 alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_8 alkanoyl, aroyl, heteroaroyl, aryl, heteroaryl, C_1-C_6 arylalkyl or C_1-C_6 heteroarylalkyl;

R^{11} is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl;

R^{12} is selected from H, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, optionally substituted with OR^7, NR^8R^9, C_3-C_6 aminocarbocycle, or C_2-C_5 aminoheterocycle;

R^{13} is independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, with the proviso that when R^7 is SO_2R^{13}, R^{13} cannot be H; and

R^{14} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, or CN.

35. A compound according to Claim 33, wherein

X is N, CH.

R^1 is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl

R^2 is H

R^3 is C_1-C_6 alkyl, trifluoromethyl, or C_1-C_6alkyl-O C_1-C_6alkyl.

R^4 is phenyl, mono-, di-, or tri-substituted C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, OR^7

R^5 is H

R^7 is methyl, ethyl, isopropyl, propyl.

36 A compound of claim 35 wherein the compound has the structure N-cyclohexyl-N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-Cyclohexyl-N'-[8-(2,6-dichloro-4-methoxy-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclohexyl-N'-[2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclohexyl-N'-[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cCyclopentyl-N'-[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[2,7-dimethyl-8-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[8-(2,6-dichloro-4-methoxy-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine.

37 A compound according to Claim 34, wherein R^{14} is H, C_1-C_4 alkyl.

38 A compound according to claim 37 wherein

R^2 is H; R^6 is H;

X is N, CH;

A is CH_2, optionally substituted with one or two of the following: F, CF_3, or methyl, ethyl, isopropyl;

B is CH_2, optionally substituted with one or two of the following: F, CF_3, or methyl, ethyl, isopropyl.

39 A compound according to claim 38 wherein

R^5 is C_1-C_7 alkyl, C_1-C_6 cycloalkyl, or C_1-C_6 cycloalkyl C_1-C_2 alkyl;

A, B is CH_2.

40 A compound according to claim 38 wherein

R^4 is selected from aryl or heteroaryl, each substituted with aryl, heteroaryl, heterocycloalkyl, and 3-, 4-, or 5-(2-oxo-1,3-oxazolidinyl), heterocycloalkyl, cyclopentenyl, cyclohexenyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl , trifluoromethylsulfonyl, C_1-C_6 alkyl-NR^8R^9, C_1-C_6 alkyl-CN , C_1-C_6 alkyl-$CONR^8R^9$, (C_1-C_4)alkyl-OR^7, C_1-C_6 alkyl-$COOR^7$and optionally substituted with 1 to 4 substituents independently selected at each occurrence from C_1-C_6 alkyl, (C_3-C_{10} cycloalkyl) C_1-C_6 alkyl, halogen, C_1-C_6 haloalkyl, trifluromethylsulfonyl, OR^7, C_1-C_6 alkyl-OR^7, NR^8R^9, C_1-C_6 alkyl-NR^8R^9, $CONR^8R^9$, C_1-C_6 alkyl.

41 A compound of claim 40 wherein

R^4 is phenyl substituted with acetylene, cyclopentenyl, cyclohexenyl, (C_1-C_4)alkyl-OR^7, C_1-C_3 alkenyl, and optionally substituted with 1 to 2 substituents independently selected at each occurrence from methyl, F, Cl, CF_3, OR^7;

R^7 is H, methyl, ethyl.

42 A compound of claim 41 where the structure is N-cyclohexyl-N'-[3-(2,6-dichloro-4-ethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[3-(2,6-dichloro-4-ethynyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclopentyl-N'-[3-(2,6-dichloro-4-cyclopent-1-enyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-cyclohexyl-N'-[3-(2,6-dichloro-4-cyclopent-1-enyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine; N-Cyclohexyl-N'-[8-(2,6-dichloro-4-cyclopent-1-enyl-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine; N-cyclohexyl-N'-[8-(2,6-dichloro-4-propenyl-phenyl)-2,7-dimethyl-pyrazolo[1,5-a][1,3,5]triazin-4-yl]-ethane-1,2-diamine.

43 A compound according to Claim 33 wherein the compound exhibits a 20-fold greater affinity for the NPY1 receptor in a assay of NPY1 receptor binding than for the CRF receptor in an assay of CRF receptor binding.

44 A compound according to Claim 33 wherein the compound exhibits a 100-fold greater affinity for the NPY1 receptor in a assay of NPY1 receptor binding than for the CRF receptor in an assay of CRF receptor binding.

45 A method for treating eating disorders and cardiovascular disorders comprising administering to a patient suffering from an eating disorder or cardiovascular disorder a compound according to Claim 33.

46 A pharmaceutical composition comprising a compound according to Claim 33 and a pharmaceutically acceptable carrier.

47 A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 33 in a container and comprising instructions for using the composition to treat a patient suffering from an eating disorder or hypertension.

48 A method for localizing NPY receptors in tissue section samples comprising: contacting with a sample of tissue a detectably-labeled compound of Claim 33 under conditions that permit binding of the compound to the sample of tissue; washing the tissue sample to remove unbound compound; and detecting the bound compound.

49 The method of Claim 48, wherein the compound is radiolabeled.

50 A method of inhibiting the binding of NPY to the NPY1 receptor, which method comprises contacting, in the presence of NPY, a solution comprising a compound of Claim 33 with cells expressing the NPY1 receptor, wherein the compound is present in the solution at a concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

51 A method for altering the signal-transducing activity of a cell surface NPY1 receptor, said method comprising contacting cells expressing such a receptor with a solution comprising a compound according to Claim 33, wherein the compound is present in the solution at a

concentration sufficient to reduce levels of NPY binding to cells expressing the NPY1 receptor in vitro.

52 A compound according to Claim 33 wherein in an assay of NPY binding the compound exhibits an K_i of 1 micromolar or less.

53 A compound according to any one of Claim 33 wherein in an assay of NPY binding the compound exhibits an K_i of 1 micromolar or less.

54 A compound according to any one of Claim 33 wherein in an assay of NPY binding the compound exhibits an K_i of 100 nanomolar or less.

55 A method for treating obesity or bulimia nervosa which comprises administering an effective amount of a compound according to Claim 33 to a patient in need thereof.

56 A method for treating hypertension which comprises administering an effective amount of a compound according to Claim 33 to a patient in need thereof.

57 A method of converting core heterocyles of formula A and B to a compound that exhibits a Ki of 5 micromolar or less in an assay of NPY receptor binding.

58 A method of treating obesity comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula as defined in claim 34 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug.

59 A method as recited in claim 58 wherein the amount of the compound in FormulaI as defined in claim 34 is about 0.01 mg/kg/day to about 50 mg/kg/day.

60 A method as recited in claim 59 wherein the mammal is female or male human.

61 A pharmaceutical composition which comprises a therapeutically effective amount of compound of claim 34 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

62 A pharmaceutical composition for the treatment of obesity which comprises a therapeutically effective amount of compound of claim 34 or a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, vehicle or diluent.

63 A pharmaceutical combination composition comprising a therapeutically effective amount of a composition comprising: (a) first compound, said first compound being a compound of claim 34, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent.

64 A method of treating obesity comprising administering to a mammal in need of such treatment: (a) first compound, said first compound being a compound of claim 34, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; (and (c) wherein the amounts of the first and second compounds result in a therapeutic effect.

65 A kit comprising: (a) first compound, said first compound being a compound of claim 34, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being a β_3 agonist, a thyromimetic, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle, diluent; and (c) means for containing said first and second unit dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

66 A pharmaceutical combination composition comprising a therapeutically effective amount of a composition comprising (a) first compound, said first compound being a compound of claim 34, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; (b) a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, insulin, metformin, acarbose, a thiazolidinedione, a glitazone, rezulin, trogitalazone, a sulfonylurea, glipazide, glyburide, or chlorpropamide; (c) a pharmaceutical carrier, vehicle, or diluent.

67 A pharmaceutical composition comprising a compound as defined in claim 34 for the treatment of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dislipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disorders, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.

68 A method of selectively inhibiting binding of NPY_1 receptors, which comprises contacting a compound of claim 33 with neuronal cells, wherein the compound is present in an amount effective to produce a concentration sufficient to selectively inhibit binding of NPY peptides to NPY_1 receptors in vitro.

SEQUENCE LISTING

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Horvath, Raymond F.
Blum, Charles
Tran, Jennifer
De Lombaert, Stephane
Hodgetts, Kevin J.
Carpino, Philip A.

<120> Amino Substituted Pyrazolo [1,5,-a]-1,5-Pyrimidines and Pyrazolo [1,5-a]-1,3,5-Triazines

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Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1040	FILED BY	Jennifer Vail
PATENT CENTER #	71844364	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kaia Parenti

Documents

TOTAL DOCUMENTS: 100

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(54) **THIAZOLE PYRAZOLOPYRIMIDINES AS CRF1 RECEPTOR ANTAGONISTS**

THIAZOLPYRAZOLOPYRIMIDINE ALS ANTAGONISTEN DES CRF1-REZEPTORS

THIAZOLE PYRAZOLOPYRIMIDINES CONVENANT COMME ANTAGONISTES DU RÉCEPTEUR DU CRF1

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(73) Proprietor: **ELI LILLY AND COMPANY**
Indianapolis, IN 46285 (US)

(72) Inventors:
- **CHEN, Zhaogen**
  Carmel, Indiana 46032 (US)
- **HAMDOUCHI, Chafiq, Hamdouchi**
  Carmel, Indiana 46032 (US)
- **HEMBRE, Erik, James**
  Indianapolis, Indiana 46202 (US)
- **HIPSKIND, Philip, Arthur**
  New Palestine, Indiana 46163 (US)
- **MYERS, Jason, Kenneth**
  Indianapolis, Indiana 46256 (US)
- **TAKAKUWA, Takako**
  Indianapolis, Indiana 46237 (US)
- **TOTH, James, Lee**
  Knightstown, Indiana 46148 (US)

(74) Representative: **Bassinder, Emma Marie**
Eli Lilly and Company Limited
European Patent Operations
Lilly Research Centre, Erl Wood Manor
Sunninghill Road
Windlesham, Surrey GU20 6PH (GB)

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- **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**
- **HE LIQI ET AL: "4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimet hyl-8-(2,4- dichlorophenyl) pyrazolo[1,5-a]-1,3,5-triaz ine: 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**

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(Cont. next page)

EP 2 094 709 B1

- 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

Description

FIELD OF THE INVENTION

[0001] This invention relates to novel thiazole pyrazolopyrimidine compounds, pharmaceutical compositions thereof, and use thereof as CRF' I receptor antagonists in the treatment of psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndrome.

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.

[0003] 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, 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.

[0004] 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 CRF I 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/hypothalmic 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 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.

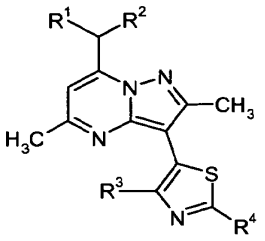
[0005] Certain pyrrolo[2,3-*d*]pyrimidines, pyrrolo[3,2-*d*]pyrimidines, pyrazolo[1,5-*a*]pyrimidines, 1,2,3-triazolo[4,5-*b*] pyridines, and pyrazolo[1,5-*a*]-1,3,5-triazines, useful as CRF antagonists, are described in WO 94/13676, WO 97/29109, WO 98/08847, and WO 98/03510. WO 00/59908 discloses certain pyrazolo[1,5-*a*] pyrimidines which are described as CRF antagonists. WO 2005/063755 discloses a genus of compounds encompassing pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]pyrimidin-2-ones, the compounds in this genus are also described as CRF antagonists. The CRF antagonists 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-*b*]pyridazine and 4-(2-butylamino)-2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)pyrazolo[1,5-*a*]-1,3,5-triazine are disclosed in J. Neuroscience, Vol. 27, No. 10, 2718-2726 (2007) and WO 02/072202, respectively. He et al. describe in J. Med. Chem., Vol. 43, 449-456 (2000) SAR studies in the pyrazolo[1,5-a]-1,3,5-triazine series leading to the discovery of the CRF antagonist 4-(1,3-dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)-pyrazolo[1,5-*a*]-1,3,5-triazine. Chen et al. in J. Med. Chem., Vol. 47, 4787-4798 (2004) describe a series of 3-pyridylpyrazolo[1,5-*a*]pyrimidines, which are described a CRF antagonists.

[0006] WO 01/23388 discloses certain amino-substituted pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]-1,3,5-triazines which are described as selective modulators of mammalian neuropeptide Y_1 (NPYI) receptor.

[0007] The present invention provides novel thiazole pyrazolopyrimidines useful as CRF1 receptor antagonists. In view of the above, it is desirable to discover new efficacious and selective antagonists of CRF 1 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 relative to known CRF antagonists such as CP154526 and NBI30775.

SUMMARY OF THE INVENTION

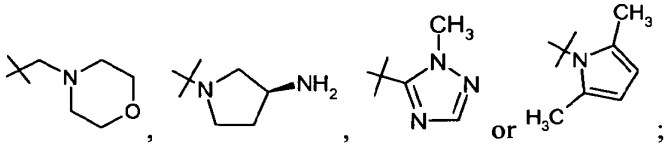
[0008] In one embodiment, the present invention provides a compound of Formula I



Formula I

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, morpholin-4-yl,



R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-; or a pharmaceutically acceptable salt thereof.

[0009] 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.

[0010] 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.

[0011] 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, pituitary or ectopic pituitary-derived tumors, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis.

[0012] In another embodiment, the present invention relates to a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in therapy.

DETAILED DESCRIPTION OF THE INVENTION

[0013] 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.

"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).

"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 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 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.

[0014] 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 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.

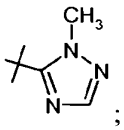
[0015] The symbol "-" in a molecular structure indicates the position of attachment for that particular substituent.

[0016] 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 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.

[0017] Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, an arylcarbonylaminoalkyl substituent is equivalent to aryl-C(O)-NH-alkyl-.

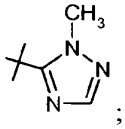
[0018] The present invention contemplates the following embodiments, which can alternatively be further combined:

(a) A compound of Formula I wherein R^1 and R^2 are ethyl;
(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, or



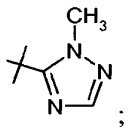
;

(g) A compound of Formula I wherein R^4 is morpholin-4-yl;
(h) A compound of Formula I wherein R^4 is



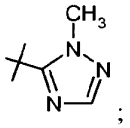
;

(i) A compound of Formula I wherein R^3 and R^b are independently C_1-C_3alkyl;
(j) A compound of Formula I wherein R^1 and R^2 are ethyl, R^3 is Cl, and R^4 is morpholin-4-yl;
(k) A compound of Formula I wherein R^1 and R^2 are *n*-propyl, R^3 is Cl, and R^4 is morpholin-4-yl;
(l) A compound of Formula I wherein R^1 and R^2 are ethyl, R^3 is Br, and R^4 is morpholin-4-yl;
(m)A compound of Formula I wherein R^1 and R^2 are *n*-propyl, R^3 is Br, and R^4 is morpholin-4-yl;
(n) A compound of Formula I wherein R^1 and R^2 are ethyl, R^3 is Cl, and R^4 is



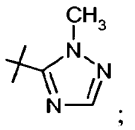
;

(o) A compound of Formula I wherein R^1 and R^2 are *n*-propyl, R^3 is Cl, and R^4 is



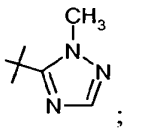
;

(p) A compound of Formula I wherein R^1 and R^2 are ethyl, R^3 is Br, and R^4 is



;

(q) A compound of Formula I wherein R^1 and R^2 are *n*-propyl, R^3 is Br, and R^4 is



;

(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 comound of Formula I, or a pharmaceutically acceptable salt thereof, for treating alcohol or substance abuse and associated withdrawal symptoms;
(u) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF 1 binding of ≤ 500 nM;
(v) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF 1 binding of ≤ 50 nM;
(w)A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF 1 binding of ≤ 5 nM;
(x) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF 1 binding of ≤ 500 nM and selectively binding to CRF1 (i.e., lower Ki) relative to CRF2;
(y) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF 1 binding of ≤ 50 nM and selectively binding to CRF 1 (i.e., lower Ki) relative to CRF2;
(z) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF I binding of ≤ 5 nM and selectively binding to CRF 1 (i.e., lower Ki) relative to CRF2; and/or
(aa) Particular exemplified compounds with superior bioavailability and pharmacokinetic profiles relative to some known CRF antagonists (e.g., CP 154526 and NBI30775), such as Example 15.

[0019] The compounds of the present invention are preferably formulated as 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).

[0020] 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 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.

[0021] The compounds of Formula I are CRF-1 antagonists and, as such, are useful for 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 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)].

[0022] 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 sclerosis, as they relate to the dysfunction of CRF neurons in the central nervous system [for a review, see: E. B. De Souze, 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 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)], 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 syndrome [Y. Tache et al., Eur J. Surg. Sups1:16-22 (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 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. 12:1503-1512 (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. Nijsen et al., Neurogastroenterol. Motil. 17: 423-432 (2005)], sleep disorders [T. M. Buckley and A. F. Schatzberg, J. Clin. Endocrinol. Metab. 90:3106-3114(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)].

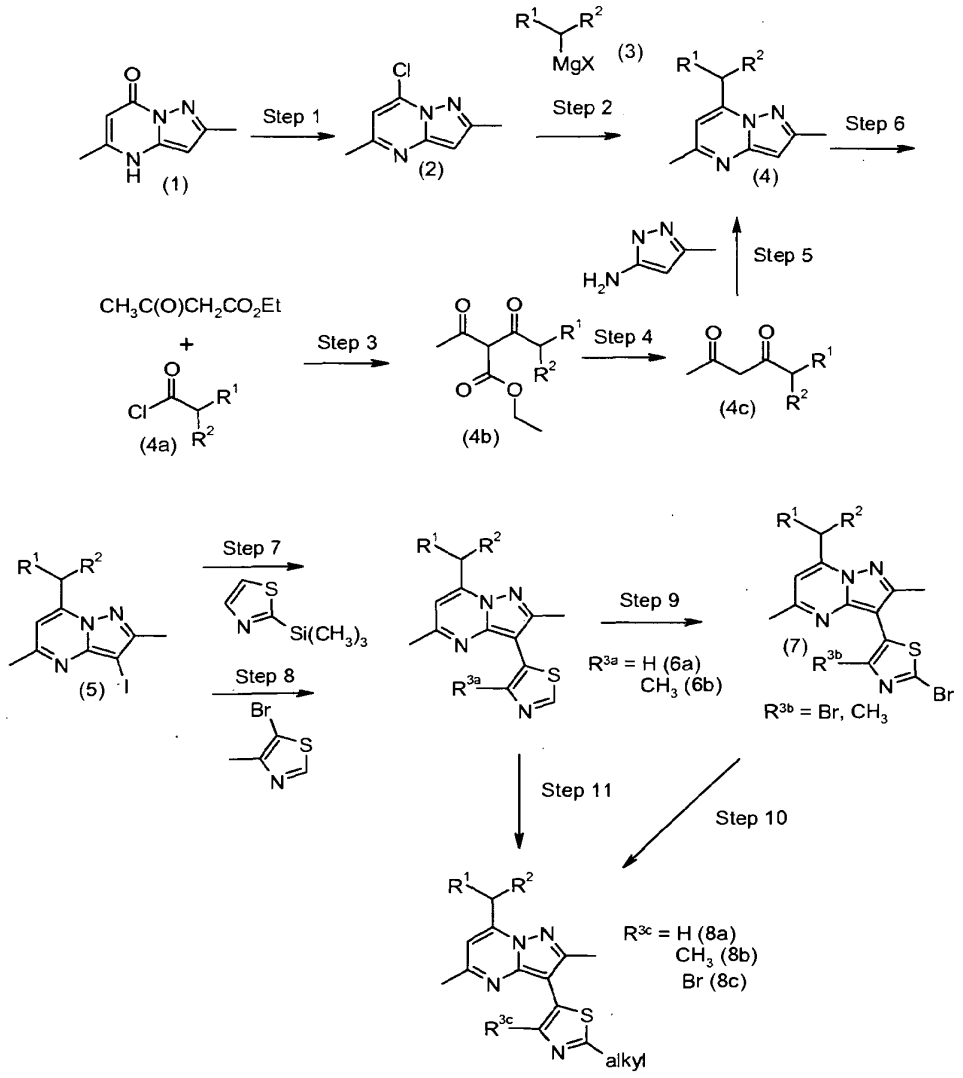
[0023] CRF receptor subtypes, CRF 1 and CRF2, have been identified and are distributed heterogeneously within the brain [D. T. Chalmers et al., TIPS 17:166-72 (1996)] thereby suggesting potential functional diversity [S. C. Heinrichs et al., Regul. Peptides 71:15 (1997)]. For example, widely distributed brain CRF1 receptor 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 et al., 1997]. A more discrete septal/hypothalmic 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 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 CRF 1 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, CRF 1 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

[0024] All of the compounds of the present invention can be chemically prepared, for 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 by conventional methods including extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallization, and the like. In the Schemes below all substituents, unless otherwise indicated, are as previously defined and suitable reagents are well known and appreciated in the art.

Scheme 1



[0025] 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.

[0026] 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 oxychloride and dimethylaniline in an inert solvent, such as toluene, at the reflux temperature of the solvent.

[0027] 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).

[0028] 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 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.

[0029] The pyrazolopyrimidine of formula (4) is functionalized to an iodo pyrazolopyrimidine of formula (5) in Step 6 using an excess ofN-iodosuccinimide in acetonitrile.

[0030] 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.; Skjaerbaek, N.; Vedso, P. 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-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).

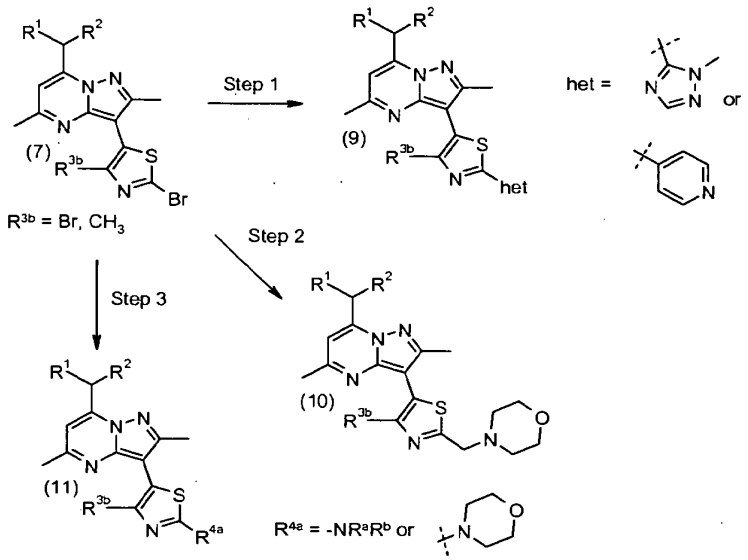
[0031] Alternatively, in Step 8, a thiazole zinc bromide is generated using 5-bromo-4-methylthiazole and zinc metal, and used in the Negishi cross-coupling essentially as described for Step 7, to provide a thiazole pyrazolopyrimidine of formula (6b).

[0032] In Scheme 1, Step 9, a thiazole of formula (6a,b) is brominated to give a bromo or dibromo thiazole of formula (7), wherein R^{3b} = 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.

[0033] 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-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.

[0034] 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-trimethylsilanyl-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-4*H*-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



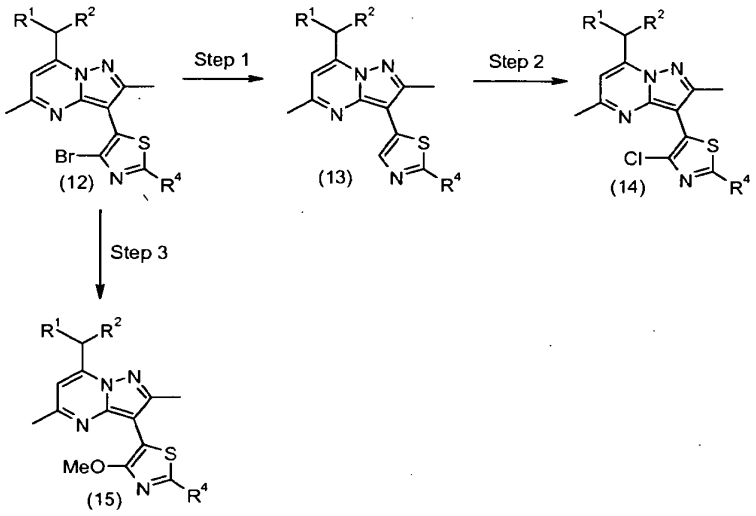
[0035] Formation of a compound of formula (9), (10), or (11) can be carried out in accordance with reactions as depicted in Scheme 2. An appropriate compound of formula (9), (10), or (11) is one in which R^1, R^2, R^a, and R^b are as defined for formula I and R^{3b} = Br or CH_3, and R^{4a} = -NR^aR^b or -N-morpholinyl and "het" is defined as depicted.

[0036] 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(diphenyl-phosphino)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.

[0037] 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 inorganic borohydride reagent such as sodium borohydride or sodium cyanoborohydride. Preferred conditions use sodium triacetoxyborohydride in an inert solvent such as dichloromethane or THF.

[0038] In Step 3, a bromothiazole of formula (7) undergoes a displacement reaction with an amine of formula -NR^3R^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

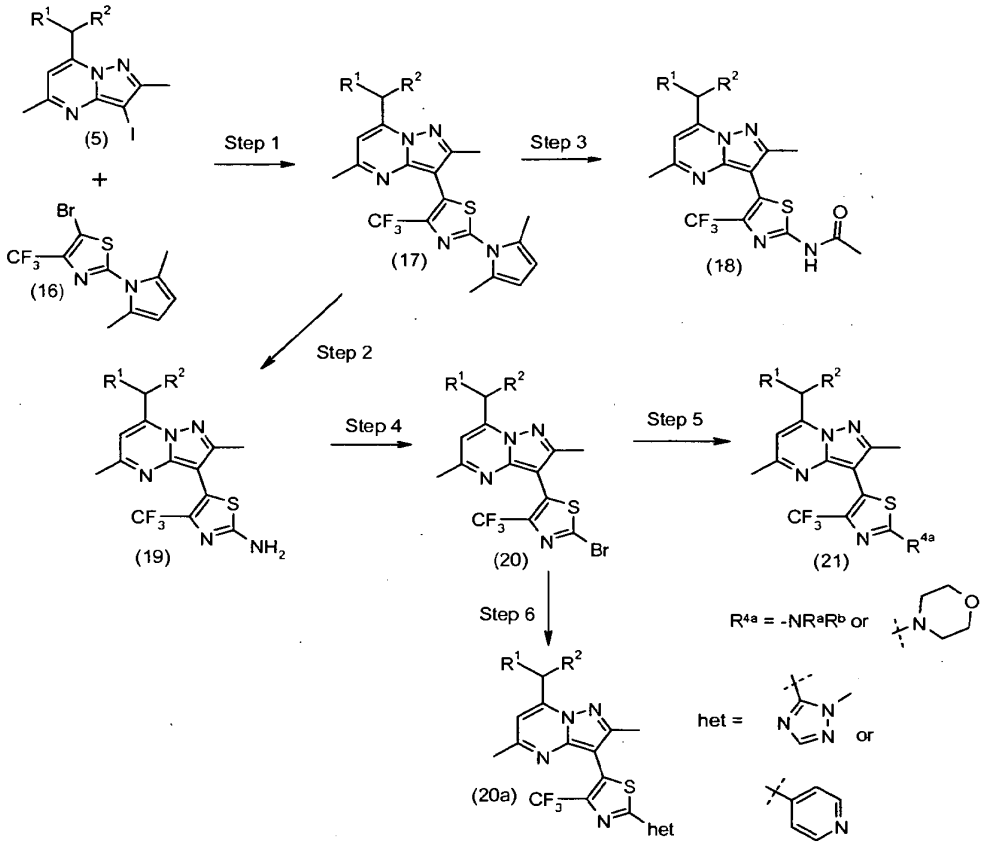


[0039] Formation of a compound of formula (13), (14), or (15) can be carried out in accordance with reactions as depicted in Scheme 3. An appropriate compound of formula (13), (14), or (15) is one in which R^1, R^2, and R^4 are as defined for formula I.

[0040] 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).

[0041] 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 inert solvent such as dimethylformamide, to provide a 4-methoxy thiazole of formula (15).

Scheme 4



[0042] 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.

[0043] 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-*t*-butylphosphine) palladium (0).

[0044] 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 used as in Step 2, with the exception that the reaction is continued for about 72 h.

[0045] 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 alkylnitrite, such as *t*-butylnitrite, and copper (II) bromide, in acetonitrile at a temperature of about 60 to 80 °C.

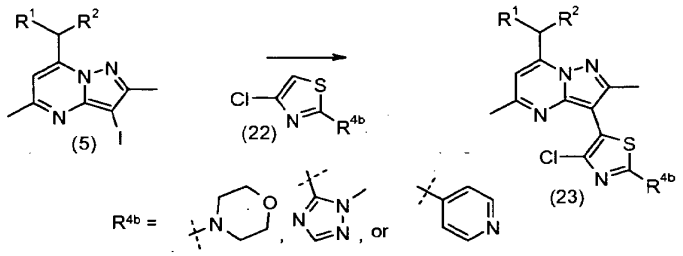
[0046] In Step 5, a 2-bromothiazole of formula (20) undergoes a displacement reaction with an amine of formula $-NR^aR^b$ or with morpholine to provide an aminothiazole of formula (21). The reaction is performed in an inert solvent, such as methanol, THF, or dioxane, or is treated neat, with an excess 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 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 and appreciated in the art (see for example, Protecting Groups in Organic Synthesis, Theodora Greene (Wiley-Interscience)).

[0047] 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 1.

[0048] 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 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).

Scheme 5

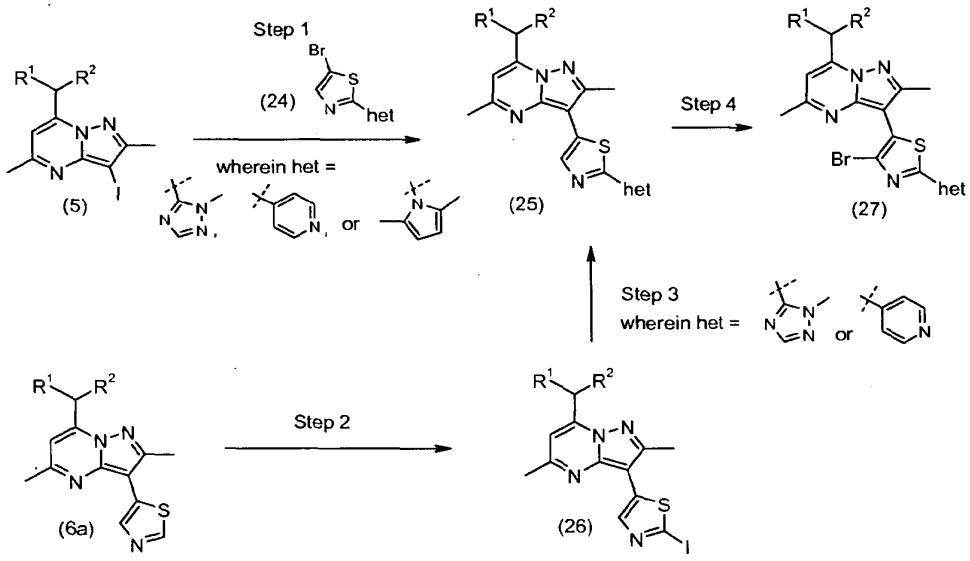


[0049] Formation of a compound of formula (23) can be carried out in accordance with reactions as depicted in Scheme 5. An appropriate compound of formula (23) is one in which R^1 and R^2 are as defined for formula I and R^{4b} is defined as depicted.

[0050] 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 about 100 - 150 °C. for 4 - 24 h.

[0051] 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 1: 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.

Scheme 6



[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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; "8" 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

[0059] 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. 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

2,5-Dimethyl-4H-pyrazolo[1,5-*a*]pyrimidin-7-one

[0060] Add ethyl acetoacetate (128 g, 0.98 mol) dropwise to an acetic acid solution (500 mL) of 5-methyl-2*H*-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

[0061] To a suspension of 2,5-dimethyl-4*H*-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 (^{35}Cl) 182.3 $(M+1)^+$.

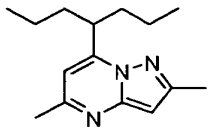
Alternate Procedure:

[0062] 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

[0063]



[0064] 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:

[0065] 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 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 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) 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

[0066] 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 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. 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.

Step 2: 5-Propyl-octane-2,4-dione

[0067] 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.

Step 3: 7-(1-Propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0068] Mix 5-propyl-octane-2,4-dione (15 g, 81.40 mmoles) 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 $MgSO_4$, filter, and concentrate under vacuum to give a crude oil (15.8 g, 79%). ^1H NMR ($CDCl_3$): 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).

[0069] 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-*a*]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

[0070] 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) ofN-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%). ^{1}H NMR (400 MHz, $CDCl_3$): 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).

[0071] 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-*a*]pyrimidine dimethyl-pyrazolo[1,5-*a*] pyrimidine	1H 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, J = 7.5 Hz, 6H).

Alternate procedure for Preparation 6:

[0072] 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 $(M+1)^+$.

Preparation 7

2-Trimethylsilanyl-thiazole

[0073] 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. ^{1}H NMR (400 MHz, $CDCl_3$) 8.13 (d, 1H, J=2.6 Hz), 7.54 (d, 1H, J = 2.6 Hz), 0.43 (s, 9H).

Preparation 8

5-Bromo-4-methylthiazole

[0074] 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, elueting with hexanes/ethyl acetate (5/1) to obtain the title compound (9.94 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 2.43 (s, 3H).

Preparation 9

Thiazole-2-carboxylic acid ethyl ester

[0075] 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 $(M+1)^+$.

Preparation 10

Thiazole-2-carboxylic acid amide

[0076] 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

[0077] 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 for 15 min, filter, and dry the solid to constant weight before using in the next step.

[0078] Add the solid isolated above (68 g) to acetic acid (680 mL) and cool the mixture to 10 °C. Add *N*-methylhydrazine (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 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 $(M+1)^+$.

Preparation 12

5-(5-Bromo-thiazol-2-yl)-1-methyl-1*H*-[1,2,4]thiazole

[0079] To a mixture of methyl-5-thiazol-2-yl-1H-[1,2,4]triazole (6.55 g; 39.4 mmol) and dimethylformamide (32 mL), add N-bromosuccinimide (14 g, 78.8 mmol) in three 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 $^{79}Br/^{81}Br$) 245/247 $(M+1)^+$.

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

[0080] Combine 5-(5-bromo-thiazol-2-yl)-1-methyl-1H-[1,2,4]triazole (6.5 g, 23.8 mmol) 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 $(M+1)^+$.

Preparation 14

2,5-Dimethyl-7-(1-propyl-butyl)-3-thiazol-5-yl-pyrazolo[1,5-*a*] pyrimidine

[0081] 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 $(M+1)^+$.

[0082] 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-*a*]pyrimidine	1H NMR (400 MHz, $CDCl_3$): d 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, J = 7.5 Hz), 0.85 (t, 6H, J = 7.5 Hz).

Alternate procedure for Preparation 15:

[0083] 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, 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 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 $(M+1)^+$.

Preparation 16

7-(1-Ethyl-propyl)-3-(2-iodo-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0084] 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 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 ofN-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 × 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

7-(1-Ethyl-propyl)-2,5-dimethyl-3-(4-methyl-thiazol-5-yl)-pyrazolo[1,5-*a*]pyrimidine

[0085] 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 tet-

rahydrofuran (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. Purify the crude product by silica gel column chromatography, elueting with hexane/ethyl acetate (3/1) to obtain the title compound (652 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): 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* = 7.3Hz). ES/MS m/z 315 $(M+1)^+$.

Preparation 17

3-(2,4-dibromo-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine

[0086] 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 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 (0-10-15-20-25-30-35-40-45-50-100% of 30% THF/hexane) to give yellow crystals (3.70 g, 79%). ES/MS m/z (^{79}Br^{81}Br) 486.7 $(M+1)^+$.

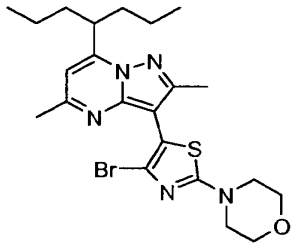
[0087] Prepare the compounds below essentially as described in Preparation 17, with the exception that dichloromethane is used as the solvent.

Ex. No.	Chemical name	Physical data
2	3-(2,4-Dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine	MS (APCI) m/z (^{79}Br^{81}Br) 459.1 $(M+1)^+$
3*	3-(2-Bromo-4-methyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine	ES/MS m/z (^{79}Br) 393 $(M+1)^+$
*Use 1.1 eq NBS and stir for 3 days.		

Example 4

3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine

[0088]



[0089] 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 $(M+1)^+$.

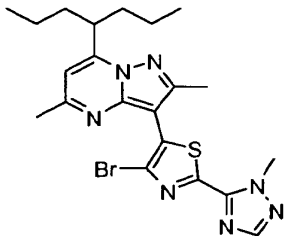
[0090] Prepare the following examples essentially as described in Example 4, using as the amine either 2.0 dimethylamine/THF or morpholine, and using THF or dioxane as the solvent. Run reactions in a sealed vessel or Schlenk tube.

Ex. No.	Chemical name	Physical data
5*	{4-Bromo-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] 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-*a*]pyrimidine	MS (APCI) m/z (^{81}Br) 466.5 $(M+1)^+$
7	{4-Bromo-S-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*] 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-*a*]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- *a*]pyrimidine	ES/MS m/z 400 $(M+1)^+$
*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-propylbutyl)-pyrazolo[1,5-*a*]pyrimidine

[0091]



[0092] 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 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 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% acetonitrileM0% THF/50% hexane) in a step gradient of 10% increments to give a white solid (0.090 g, 9%). ES/MS m/z (^{79}Br) 487.7 $(M+1)^+$.

Alternate preparation:

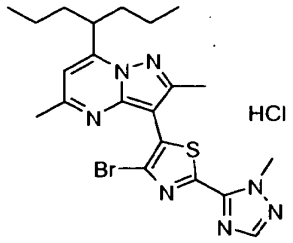
[0093] To a solution of 2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-7-(1-propyl-butyl)-pyrazolo [1,5-*a*]pyrimidine (6 g, 14.65 mmol) in acetonitrile (60 mL) add N-bromosuccinimide (2.74 g, 15.4 mmol) in one portion and stir at 22 °C for 10 h. Evaporate the solvent and dissolve 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 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 (^{79}Br/^{81}Br) 488/490 $(M+1)^+$.

Example 10a

3-[4-Bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propylbutyl)-pyrazolo[1,5-*a*]pyrimidine, hydrochloride

[0094]



[0095] Dissolve 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 (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 $(M+1)^+$; ^{1}H-NMR($CDCl_3$): 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).

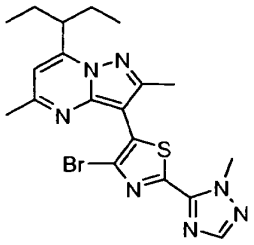
[0096] Prepare the following compound essentially as described in Example 10.

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 $(M+1)^+$
* Use 0.5 M zinc chloride in THF instead of anhydrous zinc chloride. Heat at 80 °C for 3 days.		

Example 12

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

[0097]



[0098] 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(triphenylphosine)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 (^{79}Br) 460.4 $(M+1)^+$.

Alternate preparation from Example 21:

[0099] 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): (^{79}Br/^{81}Br) 460/462 $(M+1)^+$.

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

[0100] Dissolve 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethylpropyl)-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 (1mL) 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.
[0101] Determine the stoichiometry of the salt by ion chromatography using the following HPLC conditions: column: Phenomenex Phenosphere SAX, 4.6 × 150 mm at 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).

Example 13

{4-Chloro-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidin-3-yl]-thiazol-2-yl}-dimethylamine

[0102] 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 (^{35}Cl) 406.0 $(M+1)^+$.
[0103] 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-*a*] pyrimidine	ES/MS m/z (^{35}Cl) 448.0 $(M+1)^+$
15	{4-Chloro-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*] pyrimidin-3-yl]-thiazol-2-yl}-dimethyl-amine	MS (APCI) m/z (^{35}Cl) 378.0 $(M+1)^+$

Preparation 18 2,4-dichlorothiazole

[0104] 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 : ($^{35}Cl^{35}Cl/^{35}Cl^{37}Cl^{37}Cl^{37}Cl$) 153/155/157 $(M+1)^+$.

Preparation 19

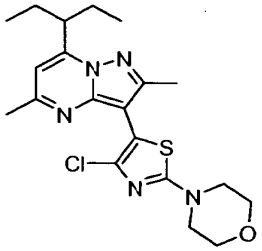
4-chloro-2-morpholino-thiazole

[0105] 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 $(M+1)^+$.

Example 16

3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0106]



[0107] 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 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 hexanes:dichloromethane:ethyl acetate (5:5:2) to provide the title compound (54 mg). MS (APCI) m/z (^{35}Cl) 420.6 $(M+1)^+$; ^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:

[0108] 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 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 $(M+1)^+$.

Example 16a

3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, hydrochloride

[0109] 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 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 $(M+1)^+$; ^{1}H NMR(CDCl3): 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

[0110] 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 $(M+1)^+$.

[0111] 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-*a*]pyrimidine	MS (APCI) m/z (^{81}Br) 424.6 $(M+1)^+$

Example 19

7-(1-Ethyl-propyl)-3-(2-methoxymethyl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0112] 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 $(M+1)^+$.

Example 20

3-(4-Chloro-2-methoxymethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0113] 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 (^{35}Cl) 379.3 $(M+1)^+$.

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

[0114] Mix 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethylpropyl)-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 $(M+1)^+$.

Alternate Preparation:

[0115] 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 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

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

[0116] 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 (^{35}Cl) 416.0 $(M+1)^+$.

Example 23

7-(1-Ethyl-propyl)-3-(4-methoxy-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0117] 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

4-Bromo-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-thiazole-2-carbaldehyde

[0118] 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-ethylpropyl)-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). 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 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 $(M+1)^+$.

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

[0119] 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 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 $(M+1)^+$.

Example 25

3-(4-Bromo-2-pyridin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0120] 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) (0.40.8 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

[0121] 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 (CH_2Cl_2) 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

[0122] 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}Br/^{81}Br) 247/249 $(M+1)^+$.

Preparation 23

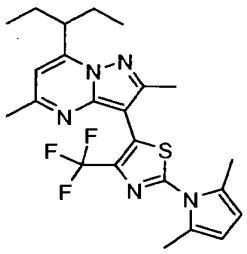
5-Bromo-2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazole

[0123] 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%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 2H), 2.27 (s, 6H).

Example 26

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

[0124]



[0125] 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×). 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 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-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamine

[0126] Add hydroxylamine (2 mL, 50% in water) to a solution of 3-[2-(2,5-dimethyl-pyrrol-l-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 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 $(M+1)^+$.

Preparation 24

3-(2-Bromo-4-trifluoromethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0127] 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, 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 ($^{79}Br/^{81}Br$) 447, 449 $(M+1)^+$.

Example 28

{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine

[0128] 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 CH_2Cl_2, to give the title compound (0.28 g, 97%). HR-ToF-MS m/z calcd for $C_{19}H_{24}F_3N_5S+H^+$ 412.1770, found: 412.1783.

[0129] 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-*a*] pyrimidine	HR-ToF-MS m/z calcd for $C_{21}H_{26}F_3N_5OS+H^+$: 454.1873, found: 454.1873, found: 454.1888

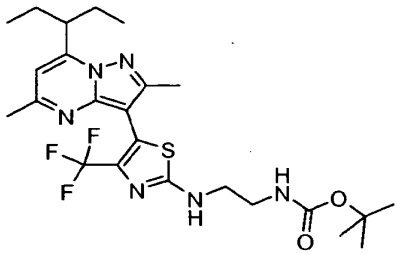
Example 30

N-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-acetamide

[0130] 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 $C_{19}H_{22}F_3N_5OS+H^+$ 426.1575, found: 426.1565.

Example 31

[0131] (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



[0132] 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 CH_2Cl_2, to give the title compound (0.11 g, 97%). ES/MS m/z 527.2 $(M+1)^+$.

[0133] 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-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-propyl-amino)-ethyl]-carbamic acid tert-butyl ester	ES/MS m/z 569.3 $(M+1)^+$
Prep. 26**	(S)-(1-{5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester	ES/MS m/z 553.3 $(M+1)^+$
Ex. 32***	*N*-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-*N*,*N*'-dipropyl-ethane-1,2-diamine, hydrochloride	ES/MS m/z 511.2 $(M+1)^+$
* 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.		

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

[0134] 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 $(M+1)^+$.

[0135] Prepare the following examples essentially as described for Example 33.

Ex. No.	Chemical name	Physical data
34	N^1-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-N^1-propyl-ethane-1,2-diamine, hydrochloride	ES/MS m/z 469.2 $(M+1)^+$
35	(*S*)-1-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-pyrrolidin-3-ylamine, hydrochloride	ES/MS m/z 453.0 $(M+1)^+$

Example A

In Vivo Potency Assessment Using Ex Vivo Binding

[0136] 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 ^{125}I-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

CRF1 Filter Binding Assay

[0137] The limitations of plasmid-based human CRF 1 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 μL) are set up as follows: 50 μL of ^{125}I-sauvagine (0.2 nM final), 50 μL compound and 100 μL CRF1 membrane (25 μg/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 μL Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 μM non-labeled sauvagine. Triplicate determinations are typically run and the median data points plotted by Graph Pad Prism.

[0138] 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 Ki (inhibition constant) below 1 μM. For example, Example 15 exhibits a Ki of 6.2 nM.

Example C

CRF2 Filter Binding Assay

[0139] 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 μL) are set up as follows: 50 μL of ^{125}I-sauvagine (0.2 nM final concentration), 50 μL compound and 100 μL CRF2 membrane (25 μg/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 μL Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 μM non-labeled sauvagine. Alternatively, compounds are evaluated using a Scintillation Proximity assay. This assay is set up as follows: 50 μL of ^{125}I-Sauvagine (0.2 nM final concentration), 50 μL compound or non-labelled sauvagine (NSB) and 100 μL

containing 250 μg wheat germ agglutinin (WGA) SPA beads and CRF2 membrane (1.5 μg/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 Graph Pad Prism. Compounds are initially screened at a fixed concentration and, if sufficient activity is noted, subsequent concentration-response curves are generated.

[0140] 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 exhibits 11% inhibition at a concentration of 50 μM. This result suggests that the compounds of the present invention are selective for the CRF 1 receptor, (relative to CRF2).

Example D

Bioavailability and Pharmacokinetic Properties

[0141] 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: Vdist = amount of drug in the body/ concentration of drug in blood or plasma (Goodman and Gillman's). For a 10 mg 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 concentration.

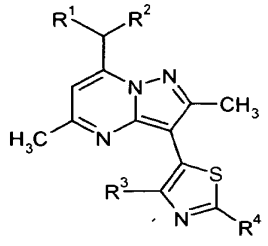
[0142] To test for volume of distribution, Male Sprague Dawley rats (N=3) are administered a single 1 mg/kg intravenous dose of compound. Multiple plasma samples are collected at time points from 0.08 to 24 hours post-dose. The plasma samples are analyzed by LC/MS/MS to determine the plasma concentrations. Plasma pharmacokinetic calculations are performed to determine the pharmacokinetic parameters including Vdist and plasma clearance (Clp).

[0143] 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 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.

[0144] 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 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 invention, when analyzed separately, exhibits a rat CLp of only 23.6 mL/min/kg.

Claims

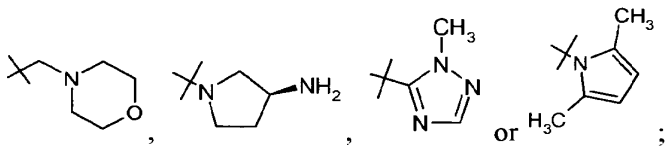
1. A compound of Formula I



Formula I

wherein:

R^1 and R^2 are independently ethyl or *n*-propel;
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl or methoxy;
R^4 is hydrogen, Br, R^aR^bN-, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,

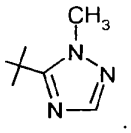


R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-; or a pharmaceutically acceptable salt thereof.

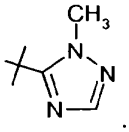
2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is Cl, Br, methyl or trifluoromethyl.

3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^3 is Cl or Br.

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 acceptable salt thereof, wherein R^4 is morpholin-4-yl or



6. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^4 is R^aR^b- and R^a and R^b are independently C_1-C_3alkyl.

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo[1,5-*a*]pyrimidine.

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-ethylpropyl)-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.

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.

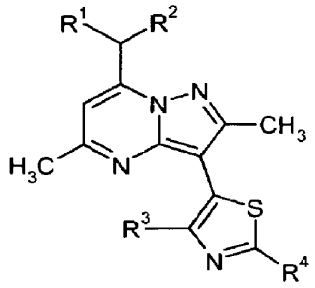
11. A compound according to any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in therapy.

12. 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.

13. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the treatment of alcohol or substance abuse.

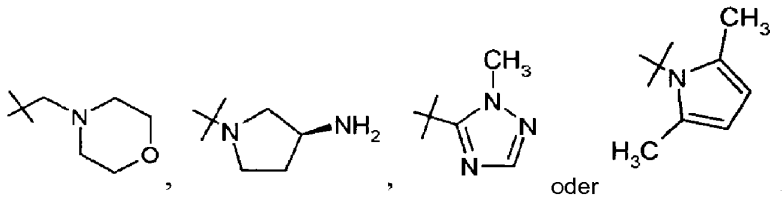
Patentansprüche

1. Verbindung der Formel I



Formel I

worin
R^1 und R^2 unabhängig voneinander für Ethyl oder n-Propyl stehen;
R^3 für Wasserstoff, Cl, Br, Methyl, Trifluormethyl oder Methoxy steht;
R^4 für Wasserstoff, Br, R^aR^bN-, Methoxymethyl, n-Butyl, Acteamido, Pyridin-4-yl, Morpholin-4-yl,

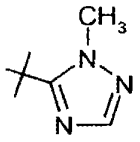


steht;
R^a und R^b unabhängig für Wasserstoff, C_1-C_3Alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$- oder $CH_3CH_2CH_2NHCH_2CH_2$- stehen;
oder ein pharmazeutisch akzeptables Salz hiervon.

2. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, worin R^3 für Cl, Br, Methyl oder Trifluormethyl steht.

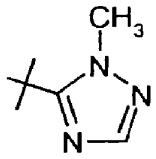
3. Verbindung nach Anspruch 1 oder 2 oder ein pharmazeutisch akzeptables Salz hiervon, worin R^3 für Cl oder Br steht.

4. Verbindung nach einem der Ansprüche 1 bis 3 oder ein pharmazeutisch akzeptables Salz hiervon, worin R^4 für R^aR^bN-, Pyridin-4-yl, Morpholin-4-yl oder



steht.

5. Verbindung nach einem der Ansprüche 1 bis 4 oder ein pharmazeutisch akzeptables Salz hiervon, worin R^4 für Morpholin-4-yl oder



steht.

6. Verbindung nach einem der Ansprüche 1 bis 4 oder ein pharmazeutisch akzeptables Salz hiervon, worin R^4 für R^aR^bN- steht und R^a und R^b unabhängig für C_1-C_3Alkyl stehen.

7. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, nämlich 3-[4-Brom-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-α]pyrimidin.

8. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, nämlich 3-(4-Brom-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-α]pyrimidin.

9. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, nämlich 3-(4-Chlor-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin.

10. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon und einen pharmazeutisch akzeptablen Hilfsstoff umfasst.

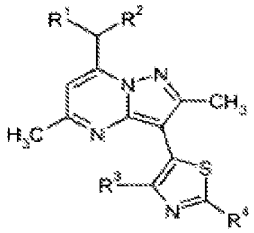
11. Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon zur Verwendung in der Therapie.

12. Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon zur Verwendung bei der Behandlung von Angst oder Depression.

13. Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon zur Verwendung bei der Behandlung von Alkohol- oder Substanzmissbrauch.

Revendications

1. Composé répondant à la formule I

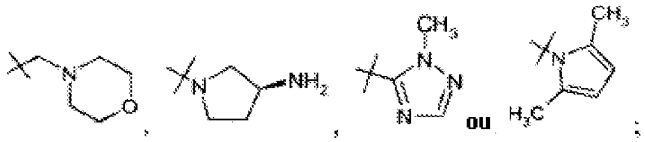


Formule I

dans laquelle :

R^1 et R^2 représentent, de manière indépendante, un groupe éthyle ou un groupe *n*-propyle ;
R^3 représente un atome d'hydrogène, un atome de chlore, un atome de brome, un groupe méthyle, un groupe trifluorométhyle ou un groupe méthoxy ;
R^4 représente un atome d'hydrogène, un atome de brome, un groupe R^aR^bN-, un groupe méthoxyméthyle, un groupe *n*-butyle, un groupe acétamido,

un groupe pyridin-4-yle, un groupe morpholin-4-yle,

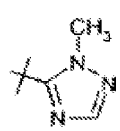


R^a et R^b représentent, de manière indépendante, un atome d'hydrogène, un groupe alkyle en C_1-C_3, un groupe $H_2NCH_2CH_2$-, un groupe $(CH_3)_3COC(O)NHCH_2CH_2$-, ou un groupe $CH_3CH_2CH_2NHCH_2CH_2$-;
ou un de ses sels pharmaceutiquement acceptables.

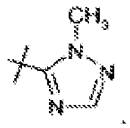
2. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, dans lequel R^3 représente un atome de chlore, un atome de brome, un groupe méthyle ou un groupe trifluorométhyle.

3. Composé selon la revendication 1 ou 2, ou un de ses sels pharmaceutiquement acceptables, dans lequel R^3 représente un atome de chlore ou un atome de brome.

4. Composé selon l'une quelconque des revendications 1 à 3, ou un de ses sels pharmaceutiquement acceptables, dans lequel R^4 représente un groupe R^aR^bN-, un groupe pyridin-4-yle, un groupe morpholin-4-yle ou un groupe



5. Composé selon l'une quelconque des revendications 1 à 4, ou un de ses sels pharmaceutiquement acceptables, dans lequel R^4 représente un groupe morpholin-4-yle ou un groupe



6. Composé selon l'une quelconque des revendications 1 à 4, ou un de ses sels pharmaceutiquement acceptables, dans lequel R^4 représente un groupe R^aR^bN- et R^a et R^b représentent, de manière indépendante, un groupe alkyle en C_1-C_3.

7. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, qui est la 3-[4-bromo-2-(2-méthyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-d iméthyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]-pyrimidine.

8. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, qui est la 3-(4-bromo-2-(2-méthyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-éthylpropyl)-2,5-diméthyl-pyrazolo[1,5-a]-pyrimidine.

9. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, qui est la 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-éthyl-propyl)-2,5-diméthyl-pyrazolo[1,5-a]pyrimidine.

10. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, et un excipient pharmaceutiquement acceptable.

11. Composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, à utiliser en thérapie.

12. Composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, à utiliser dans le traitement de l'anxiété ou de la dépression.

13. Composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, à utiliser dans le traitement de l'abus d'alcool ou d'autres drogues.

REFERENCES CITED IN THE DESCRIPTION

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(71) Applicant: **SPRUCE BIOSCIENCES, INC.** [US/US]; 548 Market Street, Suite 74589, San Francisco, California 94105 (US).

(72) Inventors: **BARNES, Christopher**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US). **KARPF, David**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US). **NOOR, Mustafa**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US).

(74) Agent: **LAMIQUIZ, Jiarong L.**; WILSON SONSINI, 650 Page Mill Road, Palo Alto, California 94304 (US).

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(54) Title: METHODS AND COMPOSITIONS FOR TREATING POLYCYSTIC OVARY SYNDROME

(57) Abstract: Polycystic ovary syndrome (PCOS) is characterized by elevated levels of androgens, cysts in the ovaries, and irregular periods. Women with PCOS present with additional symptoms, including hirsutism, alopecia, acne, infertility, weight gain, fatigue, depression and mood changes. The present disclosure provides new compounds, salts, compositions and uses thereof in the treatment of PCOS due to elevated adrenal androgens. Further, the present disclosure provides methods for treating PCOS due to elevated adrenal androgens.

WO 2022/036123 A1

METHODS AND COMPOSITIONS FOR TREATING POLYCYSTIC OVARY SYNDROME

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/064,863, filed August 12, 2020; which is referenced herein in its entirety.

BACKGROUND

[0002] Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting an estimated 12% of reproductive aged women. Women with PCOS may have polycystic ovarian morphologic features, ovulatory dysfunction in the form of infrequent or prolonged menstrual periods, and hyperandrogenism in the form of excess male hormone levels. This complex disorder has both environmental influences, such as obesity and insulin resistance, and inappropriate endocrine signaling from the hypothalamus and pituitary glands as contributors. Hyperandrogenism presents clinically as hirsutism and acne and biochemically with elevated serum androgen levels. Androgen and androgen precursors can be produced and secreted by the ovaries and also by the adrenal cortices in about the same amount in response to stimulation by pituitary derived luteinizing hormone (LH) to the ovaries and adrenocorticotropic hormone (ACTH) to the adrenal gland, respectively. Emerging data indicate that PCOS patients can be categorized according to whether the source of excessive androgen is primarily from the ovaries, namely, functional ovarian hyperandrogenism (FOH), or the adrenal glands, namely, functional adrenal hyperandrogenism (FAH), both (FOH and FAH), or neither and attributable to either insulin resistance /obesity or of unknown origin. A majority or about two-thirds of cases have functionally typical PCOS (PCOS-T) that is due to typical FOH, characterized by hyperresponsiveness of 17-hydroxyprogesterone (17-OHP). About one fifth of cases have functionally atypical FOH (PCOS-A), lacking 17-OHP hyperresponsiveness. Within these two FOH populations, about one-third may have both FOH and FAH. About 8% of PCOS cases are attributed to either obesity and the remainder are unknown or idiopathic in nature. Only about 3-5% PCOS cases are due to isolated FAH with androgen responsiveness to ACTH.

SUMMARY

[0003] Adrenal androgen excess in PCOS appears to occur independently of ovarian androgen excess, suggesting it may represent an intrinsic, and possible primary source of abnormal synthesis of adrenal androgens. Adrenal androgen excess of PCOS may not result from deficiencies in specific enzymatic steps, rather it may represent an altered pituitary responsivity to corticotropin releasing factor (CRF) and adrenocorticotropic hormone (ACTH).

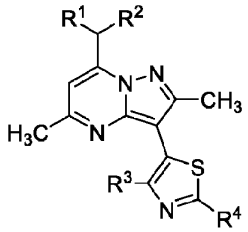
[0004] In an aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

[0005] In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

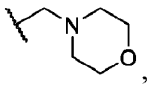
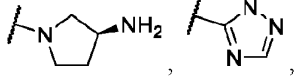
[0006] In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome (PCOS) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

[0007] In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome (PCOS) in a subject in need thereof, comprising accessing a source of excessive androgen; and administering a CRF1 antagonist or pharmaceutically acceptable salt thereof. In some embodiments, the cosyntropin is administered at a dose about 1 $\mu g/m^2$. In some embodiments, the cosyntropin is administered at a dose about 10 $\mu g/m^2$. In some embodiments, the cosyntropin is administered at a dose about 250 $\mu g/m^2$. In some embodiments, the source of excessive androgen is adrenal glands. In some embodiments, the source of excessive androgen is ovaries.

[0008] In some embodiments, the CRF_1 antagonist is a compound of Formula (I):

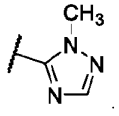


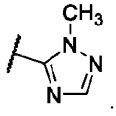
Formula (I)

or a pharmaceutically acceptable salt thereof, wherein: R^1 and R^2 are independently ethyl or *n*-propyl; R^3 is hydrogen, F, Cl, Br, methyl, trifluoromethyl, or methoxy; R^4 is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ; R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

[0009] In some embodiments, R^3 is F, Cl, Br, methyl, or trifluoromethyl.

[0010] In some embodiments, R^3 is Cl or Br.

[0011] In some embodiments, R^4 is $-NR^aR^b$, pyridin-4-yl, morpholin-4-yl, or  .

[0012] In some embodiments, R^4 is morpholin-4-yl or  .

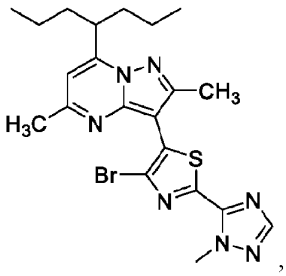
[0013] In some embodiments, R^4 is $-NR^aR^b$, and R^a and R^b are independently C_1-C_3alkyl.

[0014] In some embodiments, the CRF_1 antagonist or a pharmaceutically acceptable salt thereof is 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo[1,5-*a*]pyrimidine.

[0015] In some embodiments, the CRF_1 antagonist or a pharmaceutically acceptable salt thereof is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

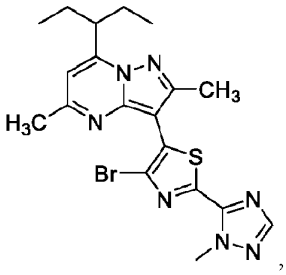
[0016] In some embodiments, the CRF_1 antagonist or a pharmaceutically acceptable salt thereof is 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

[0017] In some embodiments, the CRF_1 antagonist is



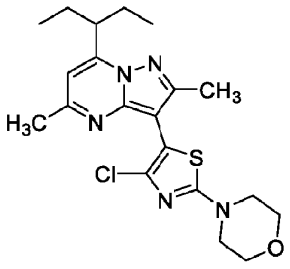
, or a pharmaceutically acceptable salt thereof.

[0018] In some embodiments, the CRF_1 antagonist is



, or a pharmaceutically acceptable salt thereof.

[0019] In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0020] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SSR125543 (crinecerfont), and SN003.

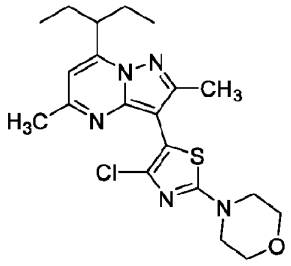
[0021] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg to about 400 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 300 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 75 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

[0022] In some embodiments, an adrenocorticotropic hormone (ACTH) level is reduced by at least 5% from baseline. In some embodiments, an adrenocorticotropic hormone (ACTH) level is reduced by at least 10% from baseline. In some embodiments, a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 5% from baseline. In some embodiments, a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 10% from baseline. In some embodiments, the androstenedione (A4) level is reduced by at least 5% from baseline. In some embodiments, the androstenedione (A4) level is reduced by at least 10% from baseline. In some embodiments, the 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 5%

from baseline. In some embodiments, the 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 10% from baseline. In some embodiments, the 11β-hydroxytestosterone (11OHT) level is reduced by at least 5% from baseline. In some embodiments, the 11β-hydroxytestosterone (11OHT) level is reduced by at least 10% from baseline.

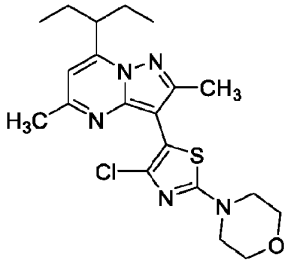
[0023] In some embodiments, a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 24 hours. In some embodiments, a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 4 weeks.

[0024] In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:



; or a pharmaceutically acceptable salt or solvate thereof.

[0025] In another aspect, the present disclosure provides methods for treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH+FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:



; or a pharmaceutically acceptable salt or solvate thereof.

[0026] In some embodiments, the Compound 3 is administered at a dose between about 1 mg/day and about 400 mg/day.

[0027] In some embodiments, the pharmaceutical composition comprises about 25 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 50 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 75 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises about 100 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments,

the pharmaceutical composition comprises about 200 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises between about 1 mg and about 300 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

[0028] In some embodiments, the pharmaceutical composition is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm to about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μm.

[0029] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule.

[0030] In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof. In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0031] In some embodiments, the subject is a pediatric patient. In some embodiments, the subject is from about 9 years old to about 18 years old. In some embodiments, the subject is from about 8 years of age to about 55 years of age. In some embodiments, the subject is an adult patient.

[0032] In some embodiments, the subject is treated for a period of about 2 weeks to about 36 weeks. In some embodiments, the subject is treated for a period of about 1 month to 12 months. In some embodiments, the subject is treated for a period of about 10 months to 50 years.

[0033] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0034] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

DETAILED DESCRIPTION

[0035] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

Polycystic Ovary Syndrome (PCOS)

[0036] Polycystic ovarian syndrome (PCOS) is a heterogeneous disorder with multiple phenotypes and is one of the most common endocrine metabolic disorders in reproductive aged women. PCOS was first diagnosed and described as a syndrome of oligo-amenorrhea and polycystic ovaries that was variably accompanied by hirsutism, acne, and obesity. There are various diagnostic criteria for adolescent and adult patients considering the core diagnostic features, such as hyperandrogenism, persistent ovulatory dysfunction, and polycystic ovarian morphology (PCOM). The exact etiology of this disorder is not entirely clear, however, both genetic and environmental factors seem to play roles in causing the disorder. Generally, PCOS presents as a phenotype reflecting a self-perpetuating vicious cycle involving neuroendocrine, metabolic, and ovarian dysfunction and is characterized by excessive ovarian and/or adrenal androgen secretion. For example, intrinsic ovarian factors such as altered steroidogenesis and factors external to the ovary such as hyperinsulinemia contribute to the excessive ovarian androgen production. The classic ovarian phenotype of enlarged ovaries with string-of-pearl morphology and theca interstitial hyperplasia reflects androgen exposure; this morphology has also been observed in women with congenital adrenal hyperplasia (CAH).

[0037] In order to attempt to understand the pathophysiology of PCOS, it is important to understand the molecular basis of steroidogenesis and androgen source, production and physiology. Under normal circumstances in women, the ovaries and adrenal glands contribute about equally to testosterone production. Approximately half of testosterone originates from direct testosterone secretion by the ovaries and adrenal glands, whereas half is produced by

peripheral conversion of circulating androstenedione, which itself arises from approximately equal ovarian and adrenal secretion. Androgen production is not under direct negative feedback regulation by the neuroendocrine system in females, as is the case for estradiol and cortisol secretion. Androgens are secreted by both the ovaries and adrenal glands in response to their respective tropic hormones, LH and ACTH. The zona reticularis of the adrenal gland resembles the theca cell compartment of the ovary in its expression of the core enzymatic pattern for androgen production.

[0038] PCOS patients can be functionally categorized as distinct subtypes based on the source of androgen excess listed in Table 1 below. Androgen excess can be derived from the ovaries, the adrenal glands, both, or neither. Primary PCOS is the most common variety of PCOS without any known cause and a proposed theory suggests that functional ovarian hyperandrogenism (FOH) along with disturbance of hypothalamo-pituitary-ovarian (HPO) axis function may be the underlying cause. Further, functional adrenal hyperandrogenism (FAH) other than HPO axis disturbance may be explained for a certain population of PCOS patients. The PCOS patients with primary FAH may experience an average 50% increase in adrenal volume that correlates with hyperandrogenemia severity.

[0039] Table 1 Functional classification of PCOS based on source of androgen excess

PCOS Functional Type	Source of Androgen	GnRHag Test 17OHP Response	DAST Testosterone Response	ACTH test DHEA Response	Prevalence Among PCOS
PCOS-T	Primary FOH (typical FOH)	High*	High in 92.5%	High in 28% (associated FAH)	67%*
PCOS-A	Primary FOH (atypical FOH)	Normal*	High	High in 30% (associated FAH)	20%
	Primary FAH (isolated FAH)	Normal	Normal	High	5%
	PCOS without FOH or FAH (PCOS-A of obesity or idiopathic PCOS-A)	Normal	Normal	Normal	8%

[0040] Test procedures to determine the source of androgen are listed below in Table 2. The ovarian hyperandrogenism of PCOS is demonstrated directly by the GnRHag test or the hCG test and in combination with the dexamethasone androgen-suppression test (DAST). The GnRHag test determines the coordinated function of the ovarian follicle. Leuprolide acetate 10 µg/kg sc (or a comparable dose of any other short-acting GnRHag) stimulates endogenous LH and FSH release that peaks at 3–4 hours and persists for 24 hours; this in turn stimulates increased secretion of sex steroids and their precursors, with serum levels peaking at 18–24 hours. In the absence of evidence of a steroidogenic block, an elevated 17OHP response is typical of PCOS. Ovarian steroidogenic enzyme deficiency, which is rare, can be detected by an abnormal pattern of steroid intermediates in response to the test. hCG is an LH analog: 5000 IU intramuscularly stimulates steroidogenic responses comparable with those of a GnRHag test at 24 hours. DAST indirectly tests for ovarian source of androgens by suppressing ACTH-dependent androgen production of androgens. In the presence of normal adrenocortical

suppression an inappropriately elevated serum testosterone post-DAST indicates an ACTH-independent source of androgen, which is ordinarily of ovarian origin.

[0041] Adrenal hyperandrogenism may be demonstrated by a rapid ACTH test: cosyntropin is administered iv and peak steroid responses occur at 15–60 minutes. An elevated DHEA post this test indicates an ACTH-dependent source of androgen, which is ordinarily of adrenal origin. The test may be performed using cosyntropin 250 μg, this is a supramaximal dose. Lower doses of cosyntropin may be used (10 μg/m2) which elicit a similar peak response. A low-dose ACTH test (1.0-μg cosyntropin) may be used and may be more physiologic. It usually elicits nearly as great a peak response that promptly wanes, and in PCOS, does not elicit such a wide spectrum of elevated steroid intermediates as do larger doses.

[0042] Table 2 Methods to determine source of female androgen excess

Test	Rationale	Method	Outcome Measures	Interpretation*
GnRHag	Endogenous LH and FSH release stimulates coordinated function of ovarian follicles	Leuprolide acetate 30 μg/kg sc (for maximum stimulation)	Ovarian steroid secretion peaks at 20–24 h	17OHP >152 ng/dL without steroidogenic block indicates typical FOH (PCOS-T)
hCG	Exogenous administration of LH analog stimulates theca-interstitial cells	hCG 3000 IU/m^2 (for maximum stimulation)	Ovarian steroid secretion peaks at 24 h	17OHP >152 ng/dL without steroidogenic block indicates typical FOH (PCOS-T)
LDAST	Long DAST: dexamethasone profoundly suppresses adrenal androgens over several days	Dexamethasone 0.5 mg OID per os × 4–5 d	Free testosterone, DHEAS, cortisol; sample early morning d 5	Free testosterone ≥8 pg/mL with DHEAS <70 and cortisol <1 μg/dL characteristic of FOH
SDAST	Short DAST: dexamethasone rapidly suppresses adrenal testosterone and cortisol	Dexamethasone 0.25 mg/m^2 per os at 12 noon	Total testosterone, cortisol, sample 4 PM (4 h)	Total testosterone >26 ng/mL, cortisol <5 μg/dL suggests FOH
ACTH	Exogenous ACTH stimulates adrenal steroidogenesis	Cosyntropin ≥10 μg/m^2 (for maximum stimulation)	DHEA,17OHP, steroid intermediates, cortisol peak at 30–60 min	DHEA 1500–3000 μg/dL without steroidogenic block indicates FAH

Corticotropin releasing factor

[0043] Currently, no single universal treatment for PCOS is available. As a result, current treatments tend to be individualized and adapted to the actual needs of the individual patient. Furthermore, treatment may be symptom-oriented. For example, targets for pharmacological treatment may include androgen excess. For PCOS patients with elevated adrenal androgens, FOH+FAH and PCOS-FAH patients, in some embodiments, pharmacological treatment, such as corticotropin releasing factor (CRF) receptor antagonist targeting ACTH production may be used.

[0044] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of

autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

[0045] CRF has been implicated in psychiatric disorders and neurological diseases including depression and anxiety, as well as the following: Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol and substance abuse and associated withdrawal symptoms, obesity, metabolic syndrome, congenital adrenal hyperplasia (CAH), Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulceration, premenstrual syndrome, sexual dysfunction, premature labor, inflammatory disorders, allergies, multiple sclerosis, visceral pain, sleep disorders, pituitary tumors or ectopic pituitary derived tumors, chronic fatigue syndrome, and fibromyalgia.

[0046] CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotropic hormone ("ACTH"), β-endorphin, and other proopiomelanocortin ("POMC")-derived peptides from the anterior pituitary. Secretion of CRF causes release of ACTH from corticotrophs in the anterior pituitary via binding to the CRF_1 receptor, a member of the class B family of G-protein coupled receptors.

[0047] Due to the physiological significance of CRF_1, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF_1 receptor remains a desirable goal and has been the subject of ongoing research and development for the treatment of anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse, and congenital adrenal hyperplasia.

[0048] The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. The middle layer, the zona reticularis is responsible for the production of androgens such as DHEA, DHEAS and androstenedione, (A4) the precursor to testosterone (T) and dihydrotestosterone (DHT). This layer is also responsible for the production of the 11-oxyandrogens, 11β-hydroxyandrostenedione (11OHA4) and 11β-hydroxytestosterone (11OHT), which are major bioactive androgens, particularly in women. Due to an unknown cause in PCOS patients with elevated androgens, the zone reticularis displays a hyperresponsiveness to ACTH resulting excessive levels of DHEA, DHEAS, 11OHA4, 11OHT and A4. The excessive ACTH stimulation causes hypertrophy of the zona reticularis resulting in

adrenal hyperplasia and clinically manifests with physical features typical of PCOS and hyperandrogenism. Reducing the stimulatory effect on the pituitary's ACTH secretion by inhibiting the CRF1 receptor is expected is reduce excessive androgen synthesis from the ACTH responsive zone of the adrenal gland in PCOS. The normalization of elevated androgen levels in the short term would be expected to ameliorate cardinal features of PCOS - hirsutism, acne and menstrual irregularities – over the long term.

Certain Definitions

[0049] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

[0050] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

[0051] The term "about" is used to indicate that a value includes 10% level of error for the device or method being employed to determine the value.

[0052] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or."

[0053] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, and preferably having from one to five carbon atoms (i.e. C_1-C_5alkyl). In some embodiments, an alkyl comprises one to four carbon atoms (i.e., C_1-C_4alkyl).). In some embodiments, an alkyl comprises one to three carbon atoms (i.e., C_1-C_3alkyl).). In some embodiments, an alkyl comprises one to two carbon atoms (i.e., C_1-C_2alkyl). In some embodiments, an alkyl comprises one carbon atom (i.e., C_1alkyl). In certain embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (iso-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (sec-butyl), 2-methylpropyl (isobutyl), 1,1-dimethylethyl (tert-butyl), or 1-pentyl (n-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more substituents such as those described herein.

[0054] The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises,"

"has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

[0055] "Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. "Administering" a pharmaceutical composition may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

[0056] By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

[0057] The term "pharmaceutical composition" means a composition comprising at least one active ingredient, such as a steroid or a pharmaceutically acceptable salt thereof or a CRF_1 antagonist or a pharmaceutically acceptable salt thereof, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

[0058] The term "supraphysiologic amount" describes glucocorticoid dose levels that are above the daily glucocorticoid requirement (production rate) found in healthy individuals.

[0059] The term "physiologic amount" describes glucocorticoid dose levels that meet the daily glucocorticoid requirement (production rate) found in healthy individuals.

[0060] The term "hydrocortisone equivalents" as used herein is understood by a person skilled in the art to be the conversion calculations needed to be considered when substituting one glucocorticoid for another as the potency and duration of action of various glucocorticoids may vary. Hence, the term "hydrocortisone equivalents" is the standard used for comparison of glucocorticoid potency.

[0061] A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the

pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

[0062] The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

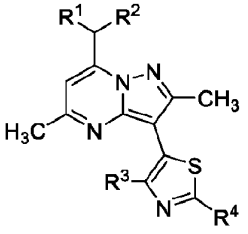
Compounds

[0063] Disclosed herein are CRF_1 antagonists or pharmaceutically acceptable salt thereof such as Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003, and SSR125543 (crinecerfont).

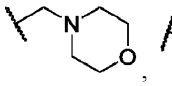
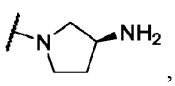
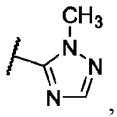
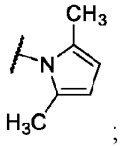
[0064] In one aspect, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: *n*-butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine hydrochloride (Antalarmin hydrochloride), *n*-butyl-N-ethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine hydrochloride (Pfizer CP154526), N-(1-Ethylpropyl)-3,6-dimethyl-2-(2,4,6-trimethylphenox y)-4-pyridinamine hydrochloride (Pfizer CP376395 hydrochloride), 5-Chloro-N-(cyclopropylmethyl)-2-methyl-*n*-propyl-N'-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride (NBI27914 hydrochloride), (7S)-6-(Cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene hydrochloride (NBI35965 hydrochloride), N-(1-Ethylpropyl)-3-methoxy-5-[2-methoxy-4-

(trifluoromethoxy)phenyl]-6-methyl-2-pyrazinamine hydrochloride (NGD 98-2 hydrochloride), 8-(6-Methoxy-2-methyl-3-pyridinyl)-2,7-dimethyl-N-[(1R)-1-methylpropyl]pyrazolo[1,5-a]-1,3,5-triazin-4-amine (Pexacerfont), 3-[6-(Dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-a]pyrimidin-7-amine hydrochloride (R 121919 hydrochloride), and N-(4-Methoxy-2-methylphenyl)-1-[1-(methoxymethyl)propyl]-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridine-4-amine (SN003), (S)-4-(2-chloro-4-methoxy-5-methylphenyl)-N-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-(prop-2-yn-1-yl)thiazol-2-amine (SSR125543).

[0065] Disclosed herein is a compound of Formula (I):



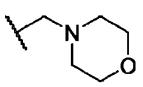
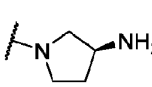
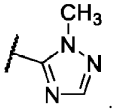
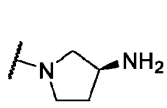
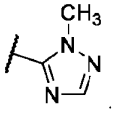
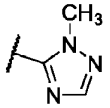
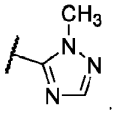
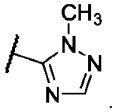
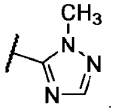
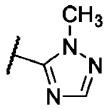
Formula (I)

or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are independently ethyl or *n*-propyl; R^3 is H, Cl, Br, methyl, trifluoromethyl, or methoxy; R^4 is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

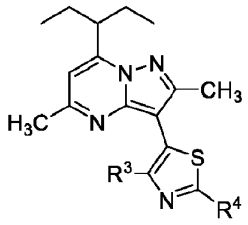
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

[0066] In some embodiments, R^1 and R^2 are independently ethyl or *n*-propyl. In some embodiments, R^1 is ethyl and R^2 is *n*-propyl. In some embodiments, R^1 is *n*-propyl and R^2 is ethyl. In some embodiments, R^1 and R^2 are both ethyl. In some embodiments, R^1 and R^2 are both *n*-propyl.

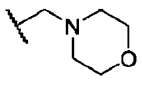
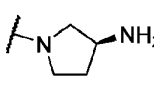
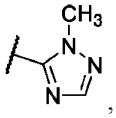
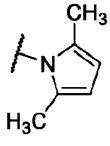
[0067] In some embodiments, R^3 is hydrogen, Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is hydrogen, Cl, Br, or methyl. In some embodiments, R^3 is hydrogen, Cl, or Br. In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is Cl. In some embodiments, R^3 is Br.

[0068] In some embodiments, R^4 is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  , or  . In some embodiments, R^4 is Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  , or  . In some embodiments, R^4 is $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is $-NR^aR^b$, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is $-NR^aR^b$,pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is morpholin-4-yl or  . In some embodiments, R^4 is morpholin-4-yl. In some embodiments, R^4 is  . In some embodiments, R^4 is $-NR^aR^b$ and R^a and R^b are independently C_1-C_3alkyl.

[0069] Disclosed herein is a compound of Formula (II):

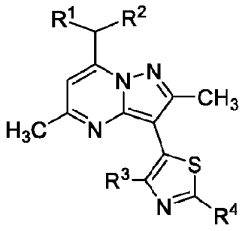


Formula (II)

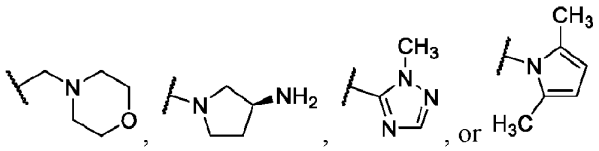
or a pharmaceutically acceptable salt thereof, wherein R^3 is H, Cl, Br, methyl, trifluoromethyl, or methoxy; R^4 is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and R^a and R^b are independently

hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$–$CH_2CH_2NHCH_2CH_2CH_3$.

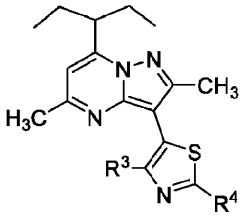
[0070] Disclosed herein is a compound of Formula (III):



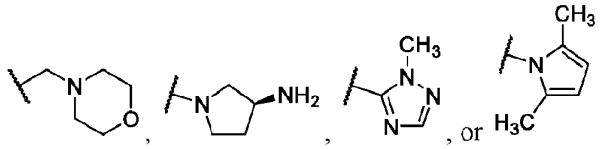
Formula (III)

or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are *n*-propyl; R^3 is H, Cl, Br, methyl, trifluoromethyl, or methoxy; R^4 is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ; and R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

[0071] Disclosed herein is a compound of Formula (IV):

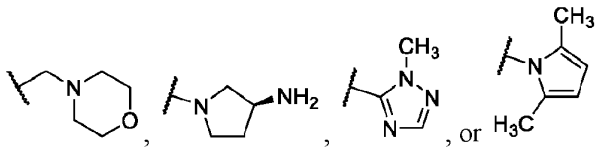
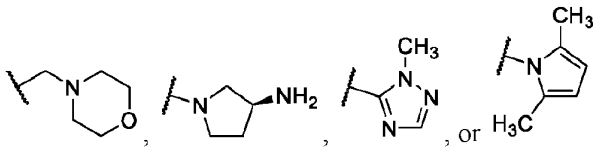
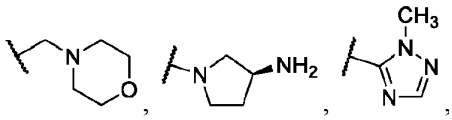
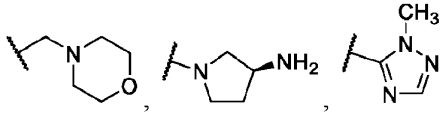
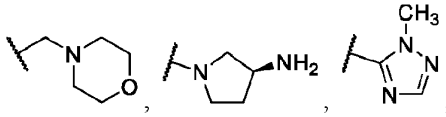


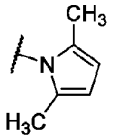
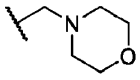
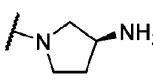
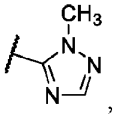
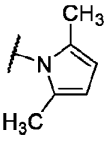
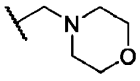
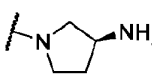
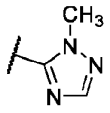
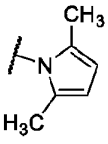
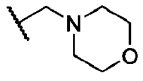
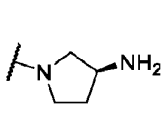
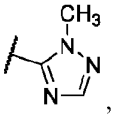
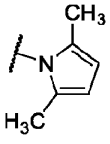
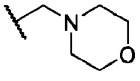
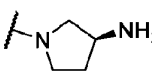
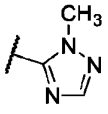
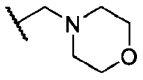
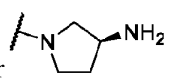
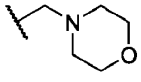
Formula IV

or a pharmaceutically acceptable salt thereof, wherein R^3 is Cl, Br, methyl, trifluoromethyl, or methoxy; R^4 is H, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ; and R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

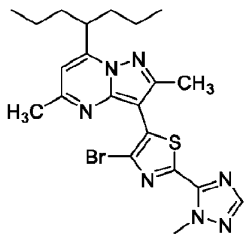
[0072] For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be Cl, Br, methyl, trifluoromethyl, or methoxy. For a compound or pharmaceutically acceptable salt of Formula

(I), (II), (III), and (IV), R^3 may be Cl, Br, methyl, or trifluoromethyl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be Cl, Br, or methyl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be Cl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be Br. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^3 may be methyl.

[0073] For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is Br, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is Br, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is Br, acetamido, pyridin-4-yl, morpholin-4-yl,  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is Br, pyridin-4-yl, morpholin-4-yl,  .

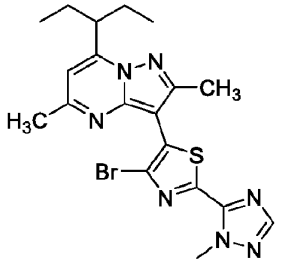
 . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is morpholin-4-yl,  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R^4 is morpholin-4-yl.

[0074] Disclosed herein is 3-[4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]pyrimidine (Compound 1) or a pharmaceutically acceptable salt thereof:



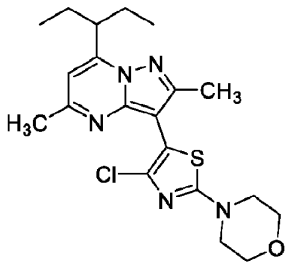
Compound 1.

[0075] Disclosed herein is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (Compound 2) or a pharmaceutically acceptable salt thereof:



Compound 2.

[0076] Disclosed herein is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine (or alternatively 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine) (Compound 3) or a pharmaceutically acceptable salt thereof:



Compound 3.

[0077] In some embodiments, 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine is referred to as Compound 3. In some embodiments, 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine is referred to as Compound 3.

[0078] In one aspect, the CRF_1 antagonist or pharmaceutically acceptable salt thereof may be an astressin. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

Pharmaceutical Compositions

[0079] Disclosed herein are pharmaceutical compositions comprising a compound or pharmaceutically acceptable salt described herein. In certain embodiments, the composition comprises a steroid or a pharmaceutically acceptable salt thereof and a CRF_1 antagonist or pharmaceutically acceptable salt thereof as disclosed above. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is exogenous glucocorticoids (GC) or a pharmaceutically acceptable salt thereof.

Dosage Form

[0080] In some embodiments, the pharmaceutical compositions described herein are provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound or pharmaceutically acceptable salt described herein that is suitable for administration to an animal, preferably mammal, subject in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

[0081] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0082] In some embodiments, the pharmaceutical compositions described herein are formulated as oral dosage forms. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules. In some embodiments, the pharmaceutical composition comprises one or more additional pharmaceutically acceptable excipients. See, e.g., Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005) for a list of pharmaceutically acceptable excipients.

Capsule

[0083] In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

[0084] In some embodiments, the capsule is formed using materials which include, but are not limited to, natural or synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, or any combinations thereof. In some embodiments, the capsule is formed using preservatives, coloring and opacifying agents,

flavorings and sweeteners, sugars, gastroresistant substances, or any combinations thereof. In some embodiments, the capsule is coated. In some embodiments, the coating covering the capsule includes, but is not limited to, immediate release coatings, protective coatings, enteric or delayed release coatings, sustained release coatings, barrier coatings, seal coatings, or combinations thereof. In some embodiments, a capsule herein is hard or soft. In some embodiments, the capsule is seamless. In some embodiments, the capsule is broken such that the particulates are sprinkled on soft foods and swallowed without chewing. In some embodiments, the shape and size of the capsule also vary. Examples of capsule shapes include, but are not limited to, round, oval, tubular, oblong, twist off, or a non-standard shape. The size of the capsule may vary according to the volume of the particulates. In some embodiments, the size of the capsule is adjusted based on the volume of the particulates and powders. Hard or soft gelatin capsules may be manufactured in accordance with conventional methods as a single body unit comprising the standard capsule shape. A single-body soft gelatin capsule typically may be provided, for example, in sizes from 3 to 22 minims (1 minims being equal to 0.0616 ml) and in shapes of oval, oblong or others. The gelatin capsule may also be manufactured in accordance with conventional methods, for example, as a two-piece hard gelatin capsule, sealed or unsealed, typically in standard shape and various standard sizes, conventionally designated as (000), (00), (0), (1), (2), (3), (4), and (5). The largest number corresponds to the smallest size. In some embodiments, the pharmaceutical composition described herein (e.g., capsule) is swallowed as a whole.

[0085] In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients. In some embodiments, the capsule is free of additional excipients.

[0086] In some embodiments, a capsule is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the capsule has a dose strength of up to 200 mg. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus II.

Tablet

[0087] Poorly soluble drugs may be difficult to formulate using standard technologies such as high shear wet granulation. Optimum delivery of poorly soluble drugs may require complex technologies such as solid solutions amorphous dispersions (hot melt extrusion or spray drying), nano-formulations or lipid-based formulations. Hydrophobic drug substances may be considered poorly soluble according to USP criteria and may be known to be difficult to granulate with water and other excipients. This is likely due to most known excipients for

immediate release formulations being water soluble or water-swellable. Making a tablet of a high dose drug substance that is poorly soluble may require a high concentration of the drug substance. However, as the drug concentration is increased above a certain level, formation of granules may become more and more difficult. Furthermore, at a certain drug load, it may become impossible.

[0088] In some embodiments, the pharmaceutical composition is formulated as a tablet.

[0089] In some embodiments, the tablet is made by compression, molding, or extrusion, optionally with one or more pharmaceutically acceptable excipient. In some embodiments, compressed tablets are prepared by compressing a compound or pharmaceutically acceptable salt described herein in a free-flowing form, optionally mixed with pharmaceutically acceptable excipients. In some embodiments, molded tablets are made by molding a mixture of the powdered a compound or pharmaceutically acceptable salt described herein, moistened with an inert liquid diluent. In some embodiments, the tablet is prepared by hot-melt extrusion. In some embodiments, extruded tablets are made by forcing a mixture comprising a compound or pharmaceutically acceptable salt described herein, through an orifice or die under controlled conditions. In some embodiments, the tablet is coated or scored. In some embodiments, the tablet is formulated so as to provide slow or controlled release of a compound or pharmaceutically acceptable salt described herein. In some embodiments, a tablet is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the tablet has a dose strength of up to 200 mg. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus II.

[0090] In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg, less than about 200 mg, less than about 100 mg or less than 50 mg. In some embodiments, the tablet has a dose strength of more than about 10 mg, more than about 50 mg, more than about 100 mg, more than about 150 mg, more than about 200 mg, or more than about 250 mg. In some embodiments, the tablet size is less than about 1000 mg for a dose strength of more than about 50 mg. In some embodiments, the tablet size is less than 800 mg for a dose strength of more than about 100 mg. In some embodiments, the tablet size is less than 600 mg for a dose strength of more than about 150 mg. In some embodiment, the tablet size is less than 400 mg for a dose strength of more than about 200 mg. In some embodiments, the tablet size is less than 400 mg for a dose strength of 100 mg. In some

embodiments, the tablet size is less than 200 mg for a dose strength of 50 mg. In some embodiments, the tablet size is less than 50 mg for a dose strength of 10 mg.

[0091] In some embodiments, more than about 20% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 24 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 12 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 6 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 3 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 2 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 90% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 100% of the tablet is dissolved in less than 60 minutes in conventional dissolution media.

[0092] In some embodiments, the tablet is produced at a commercial scale.

[0093] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[0094] In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete dry

powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone, polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

Pharmaceutically Acceptable Excipients

[0095] In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient. In some embodiments, the composition is free of pharmaceutically acceptable excipients. The term "pharmaceutically acceptable excipient", as used herein, means one or more compatible solid or encapsulating substances, which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction, which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. In some embodiments, the pharmaceutically acceptable excipient is of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal, being treated.

[0096] Some examples of substances, which can serve as pharmaceutically acceptable excipients include:

- Amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, the amino acid is arginine. In some embodiments, the amino acid is L-arginine.
- Monosaccharides such as glucose (dextrose), arabinose, mannitol, fructose (levulose), and galactose.
- Cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose.

- Solid lubricants such as talc, stearic acid, magnesium stearate, and sodium stearyl fumarate.
- Polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol.
- Emulsifiers such as the polysorbates.
- Wetting agents such as sodium lauryl sulfate, Tween®, Span , alkyl sulphates, and alkyl ethoxylate sulphates.
- Diluents such as calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose.
- Binders such as starches (corn starch and potato starch), gelatin, sucrose, hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC).
- Disintegrants such as starch, and alginic acid.
- Super-disintegrants such as ac-di-sol, croscarmellose sodium, sodium starch glycolate and crospovidone.
- Glidants such as silicon dioxide.
- Coloring agents such as the FD&C dyes.
- Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors.
- Preservatives such as benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate, phenylmercuric nitrate, parabens, and sodium benzoate.
- Tonicity adjustors such as sodium chloride, potassium chloride, mannitol, and glycerin.
- Antioxidants such as sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA.
- pH adjuster such as NaOH, sodium carbonate, sodium acetate, HCl, and citric acid.
- Cryoprotectants such as sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran.
- Cationic surfactants such as cetrimide, benzalkonium chloride and cetylpyridinium chloride.
- Anion surfactants such as alkyl sulphates, alkyl ethoxylate sulphates, soaps, carboxylates, sulfates, and sulfonates.
- Non-ionic surfactants such as polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glyol

esters, glycerol esters, sorbitan derivatives, polyethylene glycol (PEG-40, PEG-50, PEG-55), and ethers of fatty alcohols.

- Organic materials such as carbohydrate and modified carbohydrates, lactose, a-lactose monohydrate, spray dried lactose and anhydrous lactose, starch and pre-gelatinized starch, sucrose, manitol, sorbitol, cellulose, powdered cellulose and microcrystalline cellulose.
- Inorganic materials such as calcium phosphates (anhydrous dibasic calcium phosphate, dibasic calcium phosphate and tribasic calcium phosphate).
- Co-processed diluents.
- Surfactants such as sodium lauryl sulfate.
- Compression aids.
- Anti-tacking agents such as silicon dioxide and talc

Amounts

[0097] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 400 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 300 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 200 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 100 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 90 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 80 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 70 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 60 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 50 mg of a compound or pharmaceutically acceptable salt

described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 40 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 30 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 20 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 10 mg of a compound or pharmaceutically acceptable salt described herein.

[0098] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 200 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 100 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 90 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 80 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 70 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 60 mg of a compound or pharmaceutically acceptable salt described herein f. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 50 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 40 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg

and about 30 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 20 mg of a compound or pharmaceutically acceptable salt described herein.

Particle size

[0099] In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises a compound or pharmaceutically acceptable salt described herein, in the form of microparticles. In some embodiments, the microparticles have an average size from about 1 μm to about 100 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 50 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 30 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 20 μm. In some embodiments, the microparticles have an average size from about 5 μm to about 15 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 10 μm. In some embodiments, the microparticles have an average size from about 3 μm to about 10 μm. In some embodiments, the microparticles have an average size from about 4 μm to about 9 μm.

Methods of Treatment

[0100] Disclosed herein are methods of treating polycystic ovary syndrome (PCOS) in a subject in need thereof, comprising administering a compound or pharmaceutically acceptable salt described herein. In some embodiments, the subject in need thereof has PCOS-FAH. In some embodiments, the subject in need thereof has PCOS-FOH+FAH. In some embodiments, the methods described herein result in the reduction of a level of a hormone. Such hormones include deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, 17-OHP, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEAS), androstenediol, androstenedione (A4), testosterone (T), dihydrotestosterone (DHT), estrone, estradiol, estriol, 11β-hydroxyandrostenedione (11OHA4), 11β-hydroxytestosterone (11OHT), 11-ketoandrostenedione (11KA4), 11-ketotestosterone (11KT), 11β-hydroxy-5α-androstenedione (11OHDHA4), 11-keto-5α-androstenedione (11KDHA4), 11β-hydroxydihydrotestosterone (11OHDHT), 11-ketodihydrotestosterone (11KDHT) and ACTH. In some embodiments, the methods described herein result in the reduction of 17-OHP levels. In some embodiments, the methods described herein result in the reduction of A4 levels. In some embodiments, the methods described herein result in the reduction of ACTH levels. In some embodiments, the methods described herein result in the reduction of DHEA levels. In some embodiments, the methods described herein result in the reduction of DHEAS levels. In some embodiments, the methods described herein

result in the reduction of testosterone (T) levels. In some embodiments, the methods described herein result in the reduction of DHT levels. In some embodiments, the methods described herein result in the reduction of 11OHA4 levels. In some embodiments, the methods described herein result in the reduction of 11OHT levels. In some embodiments, the methods described herein result in the reduction of 11KA4 levels. In some embodiments, the methods described herein result in the reduction of 11KT levels.

[0101] Further, in some embodiments, the methods described herein result in the maintenance of the reduction of 17-OHP, A4, ACTH, DHEA, DHEAS, T, DHT, 11OHA4, 11OHT, 11KA4,and/or 11KT levels. In some embodiments, the reductions of 17-OHP, A4, ACTH, DHEA, DHEAS, T, DHT, 11OHA4, 11OHT, 11KA4 and/or 11KT levels may last for at least 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 2 years, 5 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years, or 100 years.

[0102] In some embodiments, the methods described herein result in the reduction of DHEAS levels. In some embodiments, the DHEAS level is reduced by at least about 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% from baseline. The baseline level of the DHEAS may be measured in a subject before beginning the treatment disclosed herein. In some embodiments, the DHEAS level is reduced by at least 5% from baseline. In some embodiments, the reduced DHEAS level from baseline may be maintained for at least about 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 48 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, or 30 weeks.

[0103] Further, in some embodiments, the methods described herein result in the maintenance of the reduction of 17-OHP, A4, ACTH, T, DHT, 11OHA4, 11OHT, 11KA4 and/or 11KT levels. In some embodiments, the reductions of 17-OHP, A4, ACTH T, DHT, 11OHA4, 11OHT, 11KA4 and/or 11KT levels may last for at least 24 hours, 36 hours, 48 hours, 60 hours, 72

hours, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 2 years, 5 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years, or 100 years.

[0104] In some embodiments, disclosed herein are methods for treating PCOS in a subject in need thereof, and the methods further comprise accessing a source of excessive androgen; and administering a CRF_1 antagonist or pharmaceutically acceptable salt thereof. In some embodiments, accessing a source of excessive androgen comprises measuring the primary source of excessive androgen produced in the subject suffering PCOS. In some embodiments, the primary source is the ovaries. In some embodiments, the primary source is the adrenal glands. In some embodiments, the primary source is both the ovaries and the adrenal glands. In some embodiments, the primary source is an organ that is able to produce androgen.

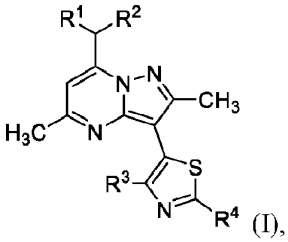
[0105] In some embodiments, cosyntropin or any other suitable hormones or chemical compounds may be administered to a subject for ACTH response in order to test for adrenal hyperandrogenism. In some embodiments, the cosyntropin is administered at a dose at least about 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 250or $\mu g/m^2$. In some embodiments, the cosyntropin is administered at a dose at about the range between the doses disclosed herein. In some embodiments, the cosyntropin is administered at a dose at most about 250, 200, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, 5, 4, 3, 2, 1 $\mu g/m^2$.

[0106] In some embodiments, the subject will be treated for a period of about 1 week to about 40 weeks. In some embodiments, the subject will be treated for a period of about 2 weeks to about 39 weeks. In some embodiments, the subject will be treated for a period of about 3 weeks to about 38 weeks. In some embodiments, the subject will be treated for a period of about 4 weeks to about 36 weeks. In some embodiments, the subject will be treated for a period of about 1 month to 12 months. In some embodiments, the subject will be treated for a period of about 10 months to 10 years. In some embodiments, the subject will be treated for a period of about 1 months to 10 years. In some embodiments, the subject will be treated for a period of about 10 months to 20 years. In some embodiments, the subject will be treated for a period of about 1 months to 20 years. In some embodiments, the subject will be treated for a period of about 10

months to 30 years. In some embodiments, the subject will be treated for a period of about 1 months to 30 years. In some embodiments, the subject will be treated for a period of about 10 months to 40 years. In some embodiments, the subject will be treated for a period of about 1 months to 40 years. In some embodiments, the subject will be treated for a period of about 10 months to 50 years. In some embodiments, the subject will be treated for a period of about 1 months to 50 years.

[0107] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SSR125543 (crinecerfont), AND SN003.

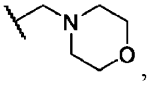
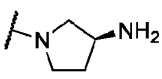
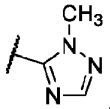
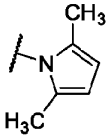
[0108] In some embodiments, the CRF_1 antagonist is a compound of Formula (I):


(I),

or a pharmaceutically acceptable salt thereof, wherein:

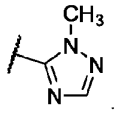
R^1 and R^2 are independently ethyl or *n*-propyl;

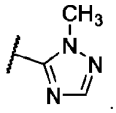
R^3 is hydrogen, F, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

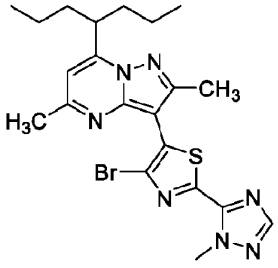
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$–$CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$–.

[0109] In some embodiments, R^3 is F, Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl.

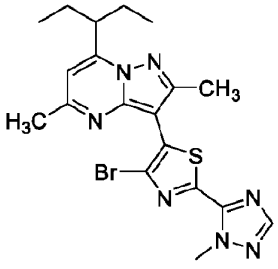
[0110] In some embodiments, R^4 is Br, $-NR^aR^b$–NR^aR^b, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is morpholin-4-yl or


. In some embodiments, R^4 is hydrogen, Br, $-NR^aR^b$ and R^a and R^b are independently C_1-C_3alkyl.

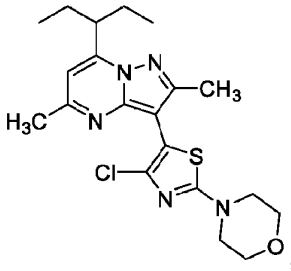
[0111] In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

[0112] In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

[0113] In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

[0114] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg to about 200 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

[0115] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is

administered in a dose of about 40 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 30 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 20 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 15 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject. In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg total daily dose to the subject.

[0116] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm to about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μ.

[0117] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

[0118] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

[0119] In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0120] In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 1 to about 8 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 to about 7 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or

a tablet as to provide a Tmax of about 2 to about 6 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 3 to about 5 hours in a subject.

[0121] In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 8 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 7 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 6 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 5 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 4 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 3 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 hours in a subject. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 1 hour in a subject.

[0122] In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof once a month, twice a month, three times a month, once a week, twice a week, three times a week, once every two days, once a day, twice a day, three times a day, or four times a day. In some embodiments, the methods described herein administer CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof twice a day.

[0123] In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, CRF_1 antagonist or pharmaceutically acceptable salt is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1500 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1400 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1300

mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1100 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 900 mg/day. In some embodiments, Compound 3 is administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 60 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 70 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 80 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 90 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 100 mg/day and about 800 mg/day. In some embodiments, Compound 3 is administered at a dose between about 100 mg/day and about 700 mg/day. In some embodiments, Compound 3 is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 3 is administered at a dose between 150 mg/day and about 600 mg/day. In some embodiments, Compound 3 is administered at a dose between 200 mg/day and about 600 mg/day. In some embodiments, Compound 3 is administered at a dose between 200 mg/day and about 500 mg/day. In some embodiments, Compound 3 is administered at a dose between 200 mg/day and about 400 mg/day. In some embodiments, Compound 3 is administered at a dose between 25 mg/day and about 200 mg/day.

[0124] In some embodiments, Compound 3 is administered at a dose of about 500 mg/day. In some embodiments, Compound 3 is administered at a dose of about 400 mg/day. In some embodiments, Compound 3 is administered at a dose of about 300 mg/day. In some embodiments, Compound 3 is administered at a dose of about 200 mg/day. In some embodiments, Compound 3 is administered at a dose of about 150 mg/day. In some embodiments, Compound 3 is administered at a dose of about 100 mg/day. In some embodiments, Compound 3 is administered at a dose of about 50 mg/day.

[0125] In some embodiments, about 50 mg to about 1600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 1600 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of CRF_1

antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 800 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 600 mg of CRF_1 antagonist or pharmaceutically acceptable salt is administered per day. In some embodiments, about 300 mg to about 600 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

[0126] In some embodiments, less than about 2000 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1200 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1000 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 800 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some

embodiments, less than about 600 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 500 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 400 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 300 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 200 mg CRF_1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day.

[0127] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein wherein the subject is in the fed state. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein wherein the subject is in the fasted state.

[0128] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

[0129] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 4 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 3 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 2 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 1 hour before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 30 mins before sleep.

[0130] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

[0131] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 11 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 10 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 9 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 8 pm at night.

[0132] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in combination with eflornithine and/or retinoids. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in combination with contraceptive pills containing androgen receptor blockers such as cyproterone acetate, spironolactone, flutamide, or 5α-reductase inhibitors.

[0133] In some embodiments, the levels of DHEA, DHEAS, A4, 11OHA4, T, 11OHT, DHT and/or ACTH in the subject are determined from a biological sample from the subject. In some embodiments, the biological sample is selected from the group of blood, blood fractions, plasma, serum, urine, other types of bodily secretions, and saliva. In some embodiments, the biological sample is obtained non-invasively.

[0134] In some embodiments, the subject is a pediatric patient. In some embodiments, the subject is an adolescent. In some embodiments, the subject is from about 8 years old to about 18 years old. In some embodiments, the subject is an adult patient. In some embodiments, the subject is from about 18 years old to about 55 years old. In some embodiments, the subject is from about 18 years old to about 50 years old.

[0135] In some embodiments, the steroid and the CRF_1 antagonist are administered concurrently. In some embodiments, the steroid and the CRF_1 antagonist are administered in one pharmaceutical composition. In some embodiments, the steroid and the CRF_1 antagonist are administered concurrently in separate pharmaceutical compositions. In some embodiments, the steroid and the CRF_1 antagonist are administered sequentially.

EXAMPLES

[0136] The following examples further illustrate the invention but should not be construed as in any way limiting its scope. In particular, the processing conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

[0137] All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

Example 1 – Reduction of DHEAS level in a subject who has polycystic ovary syndrome (PCOS) and elevated adrenal androgens

[0138] Study Compound 3 in a double-blind, proof-of-concept study, evaluating the safety and efficacy of repeated doses of Compound 3 in adults with elevated adrenal androgens, PCOS-FAH or PCOS-FAH+FOH. After screening, eligible subjects with elevated adrenal androgens documented by elevated DHEAS will be randomized to either a compound 3 dose escalation arm or matching placebo arm.

[0139] The study is planned as a 3-period study with a duration of 4 weeks for Periods 1 and 2 and a duration of 8 weeks in Period 3 for a total treatment duration of 16 weeks. Subjects randomized to the compound 3 dose escalation arm will be treated with escalating doses of 50-mg, 100-mg or 200 mg based on achieving a DHEAS positive response criteria within each treatment period. Subjects not meeting the criteria will be dose escalated to the next highest dose in the preceding period. Subjects meeting the criteria will remain on their current dose level. Placebo subjects will remain on placebo through the full 16 weeks.

[0140] The population are composed of approximately 40 patients, who receive Compound 3 or matching placebo daily for up to 16 weeks. Compound 3 is administered as an oral daily dose. Patients are undergo PK/PD or PD only assessments, approximately every 2 weeks. A follow-up outpatient visit occurs 30 days after the last dose.

[0141] Study Design

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 2
- Interventional Study Model: Randomized
- Number of Arms: 2
- Masking: Masking of Study drug
- Allocation: Randomized (1:1)
- Enrollment: 40

Arms and Interventions:

Arms	**Assigned Intervention**
Arm 1	Drug: Compound 3 dose escalation (50, 100 and 200-mg)
Arm 2	Drug: Matching Placebo

Outcome Measures

Primary Outcome Measures:

1. Safety and tolerability of Compound 3 in patients with elevated adrenal androgens (adverse effects, serious adverse effects, clinical laboratory parameters, etc.)

[Time Frame: 16 weeks]

Secondary Outcome Measures:

2. Proportion of subjects with:

   a. ≥ 30% change from baseline in dehydroepiandrosterone sulfate (DHEAS)

   b. DHEAS <upper limit of normal (ULN)

   c. DHEAS <75th percentile of normal range (Q3)

[Time Fame: 4 to up to 16 weeks]

3. Pharmacokinetics of compound 3

[Time Frame: 4 weeks]

Exploratory Outcome Measure:

4. Changes in PD markers: Changes in cortisol, ACTH, DHEAS, DHEA, A4, T, 17-OHP, 11OHA4, 11OHT, 11KA4, 11KT

[Time Frame: up to 16 weeks]

Eligibility

- Minimum Age: 18 Years
- Maximum Age: 30 years
- Sex: Female only
- Gender Based: Yes
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Female subjects 18 to 30 years old, inclusive
- Subjects must have documented PCOS according to the NIH (1990) criteria
- BMI ≤38 kg/m^2
- DHEAS level > age matched reference ULN at Screening
- Evidence of DHEA hyperresponsiveness to ACTH stimulation during Screening

Exclusion Criteria:

- Has a BMI >38kg/m^2
- Has PCOS-FOH
- Has HbA1c > 6.5% or Fasting plasma glucose >126 mg/dL
- Has a history that includes bilateral adrenalectomy or hypopituitarism
- Has a history of allergy or hypersensitivity to tildacerfont or any other CRF_1 receptor antagonist
- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant uncontrolled psychiatric disorder
- Clinically significant abnormal laboratory finding or assessment
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

[0142] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

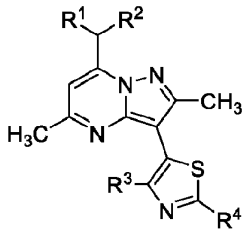
CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH + FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

2. A method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a CRF1 antagonist or pharmaceutically acceptable salt thereof.

3. The method of any of claims 1-2, wherein said CRF_1 antagonist is a compound of Formula (I):

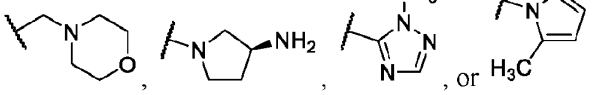


Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

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

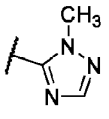
R^3 is hydrogen, F, Cl, Br, methyl, trifluoromethyl, or methoxy;

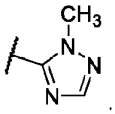
R^4 is hydrogen, Br, $-NR^aR^b$, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)OC(CH_3)_3$, or $-CH_2CH_2NHCH_2CH_2CH_3$.

4. The method of claim 3, wherein R^3 is F, Cl, Br, methyl, or trifluoromethyl.

5. The method of claim 3 or claim 4, wherein R^3 is Cl or Br.

6. The method of any one of claims 4 to 5, wherein R^4 is $-NR^aR^b$, pyridin-4-yl, morpholin-4-yl, or  .

7. The method of any one of claims 4 to 6, wherein R^4 is morpholin-4-yl or  .

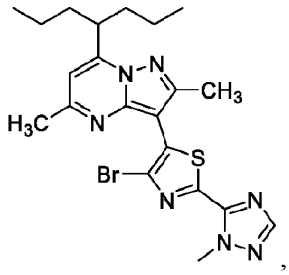
8. The method of any one of claims 4 to 6, wherein R^4 is $-NR^aR^b$, and R^a and R^b are independently C_1-C_3alkyl.

9. The method of claim 4, wherein said CRF_1 antagonist or a pharmaceutically acceptable salt thereof is 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo[1,5-*a*]pyrimidine.

10. The method of claim 4, wherein said CRF_1 antagonist or a pharmaceutically acceptable salt thereof is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

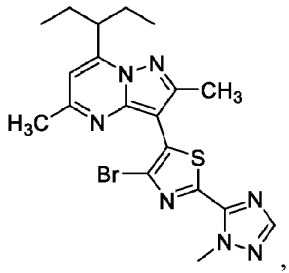
11. The method of claim 4, wherein said CRF_1 antagonist or a pharmaceutically acceptable salt thereof is 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

12. The method of claim 4, wherein said CRF_1 antagonist is



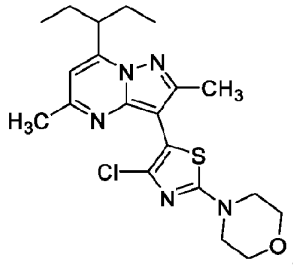
, or a pharmaceutically acceptable salt thereof.

13. The method of claim 4, wherein said CRF_1 antagonist is



, or a pharmaceutically acceptable salt thereof.

14. The method of claim 4, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

15. The method of any of claims 1-2, wherein said CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, CP-154,526, CP-376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SSR125543 (crinecerfont), and SN003.

16. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg to about 400 mg total daily dose to the subject.

17. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 300 mg total daily dose to the subject.

18. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

19. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject.

20. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject.

21. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 75 mg total daily dose to the subject.

22. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject.

23. The method of any one of claims 1-15, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject.

24. The method of any one of claims 1-15, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject.

25. The method of any one of claims 1-24, wherein the CRF_1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

26. The method of any one of claims 1-25, wherein an adrenocorticotropic hormone (ACTH) level is reduced by at least 5% from baseline.

27. The method of any one of claims 1-25, wherein an adrenocorticotropic hormone (ACTH) level is reduced by at least 10% from baseline.

28. The method of any one of claims 1-25, wherein a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 5% from baseline.

29. The method of any one of claims 1-25, wherein a dehydroepiandrosterone sulfate (DHEAS) level is reduced by at least 10% from baseline.

30. The method of any one of claims 1-25, wherein androstenedione (A4) level is reduced by at least 5% from baseline.

31. The method of any one of claims 1-25, wherein androstenedione (A4) level is reduced by at least 10% from baseline.

32. The method of any one of claims 1-25, wherein 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 5% from baseline.

33. The method of any one of claims 1-25, wherein 1β-hydroxyandrostenedione (11OHA4) level is reduced by at least 10% from baseline.

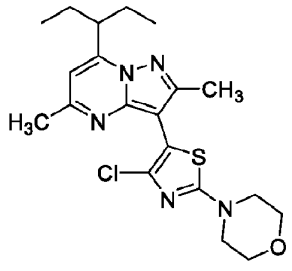
34. The method of any one of claims 1-25, wherein 11β-hydroxytestosterone (11OHT) level is reduced by at least 5% from baseline.

35. The method of any one of claims 1-25, wherein 11β-hydroxytestosterone (11OHT) level is reduced by at least 10% from baseline.

36. The method of any one of claims 25-35, wherein a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 24 hours.

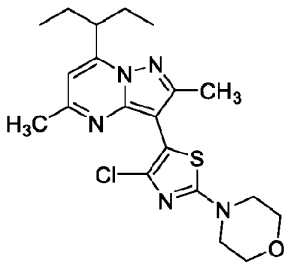
37. The method of any one of claims 25-35, wherein a reduced ACTH, DHEAS, A4, 11OHA4 or 11OHT level from baseline is maintained for at least 4 weeks.

38. A method of treating polycystic ovary syndrome with functional adrenal hyperandrogenism (PCOS-FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:



; or a pharmaceutically acceptable salt or solvate thereof.

39. A method of treating polycystic ovary syndrome with functional ovarian hyperandrogenism and functional adrenal hyperandrogenism (PCOS-FOH+FAH) in a subject in need thereof, comprising administering a pharmaceutical composition comprising Compound 3:



; or a pharmaceutically acceptable salt or solvate thereof.

40. The method of either claim 38 or claim 39, wherein Compound 3 is administered at a dose between about 1 mg/day and about 200 mg/day.

41. The method of any of claims 38-40, wherein the pharmaceutical composition comprises between about 1 mg and about 400 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

42. The method of claim 41, wherein the pharmaceutical composition comprises about 25 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

43. The method of claim 41, wherein the pharmaceutical composition comprises about 50 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

44. The method of claim 41, wherein the pharmaceutical composition comprises between about 75 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

45. The method of claim 41, wherein the pharmaceutical composition comprises about 100 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

46. The method of claim 41, wherein the pharmaceutical composition comprises about 200 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

47. The method of claim 41, wherein the pharmaceutical composition comprises about 300 mg of Compound 3, or a pharmaceutically acceptable salt or solvate thereof.

48. The method of any one of claims 1-47, wherein the pharmaceutical composition is in the form of microparticles.

49. The method of claim 48, wherein the average size of the microparticles is between about 1 μm to about 20 μm.

50. The method of claim 48, wherein the average size of the microparticles is between about 5 μm to about 15 μm.

51. The method of claim 48, wherein the average size of the microparticles is less than about 10 μm.

52. The method of any of claims 1-47, wherein the pharmaceutical composition is in the form of a capsule or a tablet.

53. The method of claim 52, wherein the capsule is a hard gelatin capsule.

54. The method of claim 52, wherein the capsule is a soft gelatin capsule.

55. The method of any one of claims 52-54, wherein the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

56. The method of any one of claims 52-54, wherein the pharmaceutical composition is free of additional excipients.

57. The method of any one of claims 52-54, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

58. The method of claim 52, wherein the pharmaceutical composition is in the form of a tablet.

59. The method of claim 58, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

60. The method of any one of claims 1-59, wherein the subject is a pediatric patient.

61. The method of any one of claims 1-59, wherein the subject is from about 9 years old to about 18 years old.

62. The method of any one of claims 1-59, wherein the subject is from about 8 years of age to about 55 years of age.

63. The method of any one of claims 1-59, wherein the subject is an adult patient.

64. The method of any of claims 1-63, wherein said subject is treated for a period of about 2 weeks to about 36 weeks.

65. The method of any of claims 1-63, wherein said subject is treated for a period of about 1 month to 12 months.

66. The method of any of claims 1-63, wherein said subject is treated for a period of about 10 months to 50 years.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/45780

A. CLASSIFICATION OF SUBJECT MATTER

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

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

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2017/0333126 A1 (Medtronic Ardian Luxembourg S.a.r.l.) 23 November 2017 (23.11.2017); abstract	1-4, 9-15, 38-40
A	US 2010/0222339 A1 (Chen et al.) 02 September 2010 (02.09.2010); abstract, para [0144]	1-4, 9-15, 38-40
A	US 2018/0110554 A1 (Ziva Medicinal, Inc.) 26 April 2018 (26.04.2018); abstract	1-4, 9-15, 38-40
A	WO 2019/036472 A1 (SPRUCE BIOSCIENCES, INC.) 21 February 2019 (21.02.2019); entire document	1-4, 9-15, 38-40
A	US 2013/0045979 A1 (Sanfilippo) 21 February 2013 (21.02.2013); entire document	1-4, 9-15, 38-40

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2021	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 Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/45780

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-8, 16-37, 41-66
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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PCT

(10) International Publication Number
WO 2005/079868 A2

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(21) International Application Number: PCT/GB2005/000432

(22) International Filing Date: 9 February 2005 (09.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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(71) Applicants *(for all designated States except US)*: **SB PHARMCO PUERTO RICO INC** [US/US]; The Prentice Hall Corp. System of PR Inc, c/o FGR Corporate Services Inc, BBV Tower 8th Floor, 254 Munoz Rivera Avenue, San Juan, PUERTO RICO 009 (US). **NEUROCRINE BIOSCIENCES INC** [US/US]; 12790 El Camino Real, San Diego, California 92130 (US).

(71) Applicant *(for MG only)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SLEE, Deborah** [US/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, California 92130 (US). **GRIGORIADIS, Dimitri** [CA/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, CA 92130 (US). **WILLIAMS, John** [US/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, CA 92130 (US).

(74) Agent: **DOLTON, Peter**; GlaxoSmithKline, CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CRF RECEPTOR ANTAGONISTS, THEIR PREPARATIONS, THEIR PHARMACEUTICAL COMPOSITION AND THEIR USES

(57) Abstract: CRF receptor antagonists are disclosed which have utility in the treatment of a variety of disorders, including the treatment of disorders manifesting hypersecretion of CRF in a warm-blooded animals. CRF receptor antagonists which are labeled with a positron emitting isotope for use in PET are also disclosed.

WO 2005/079868 A2

CRF RECEPTOR ANTAGONISTS, THEIR PREPARATION, THEIR PHARMACEUTICAL COMPOSITION AND THEIR USES

TECHNICAL FIELD

This invention relates generally to CRF receptor antagonists their preparation, their pharmaceutical composition and their uses. CRF receptor antagonists are disclosed which have utility in the treatment of a variety of disorders, including the treatment of disorders manifesting hypersecretion of CRF in a warm-blooded animals. CRF receptor antagonists which are labeled with a positron emitting isotope for use in PET are also disclosed.

BACKGROUND OF THE INVENTION

Positron Emission Tomography (PET) is a non-invasive imaging technology where a compound labeled with a positron-emitting isotope is administered to provide an in-situ image of the binding of the positron-emitting compound. The image can be used to determine localization and quantification of specific areas where the labeled compound binds providing diagnostic and drug discovery applications. Positron emitting isotopes generally used for PET include ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{76}Br and ^{124}I. The ^{13}N and ^{15}O isotopes have very short half lives limiting their usefulness. ^{76}Br and ^{124}I have half lives of 16.3 hours and 4.2 days respectively which would allow easy production of labeled CRF antagonists but the addition of the large halogen group changes the activity of the compound and adds unwanted lipophilicity. ^{11}C has a relatively short 20.5 minute half life but ease of incorporating ^{11}C into a PET compound makes this a useful isotope. ^{18}F has a half life of 110 minutes which allows sufficient time for incorporation of the isotope into a tracer, purification and administration into a subject.

The incorporation of a positron emitting isotope into a Corticotropin-releasing factor (CRF) antagonist may allow for the use of PET imaging in determining the binding of labeled antagonists to CRF receptors. CRF is a 41 amino acid peptide which has been found to produce profound alterations in endocrine, nervous and immune

system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotropic hormone ("ACTH"), ß-endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., *Science 213*:1394-1397, 1981). 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). 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 system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.

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. 278*:332, 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 suggests 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 suggests 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.

The administration of CRF antagonist which has been labeled with a positron emitting isotope may permit the use of PET imaging to provide an in situ evaluation of the labeled antagonist's binding characteristics in the brain. The antagonist should possess several characteristics such as specific binding to CRF receptors, high brain penetration and the ability to be labeled with a positron emitting isotope as the ultimate step in the synthesis.

U.S. Patent Nos. 6,514,982, 6,531,475, 6,664,261 and PCT application WO98/03510 describe CRF antagonists for use in treating various CRF mediated diseases. The synthesis of certain pyrrolopyrimidines as PET ligands for the CRF receptor has also been described. (L. Martarello et al., *Nuclear Medicine and Biology*, **28** (2001) 187-195).

While significant strides have been made toward achieving CRF regulation through administration of CRF receptor antagonists, there remains a need in the art for effective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as methods relating to the use thereof to treat, for example, stress-related disorders. The used of CRF antagonists bearing a Positron emitting isotope as diagnostic and drug discovery tools is also addressed. The present invention fulfills these needs, and provides other related advantages.

SUMMARY OF THE INVENTION

In brief, this invention is generally directed to CRF receptor antagonists 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(S)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl}amino)pyrazolo[2,3-a]pyrimidine and 6-(cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-(S)-ethyl-7,8-dihydro-4-methyl-6H-

1,3,6,8a-tetraazaacenaphthylene, including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof.

The CRF receptor antagonists of this invention may be radiolabeled and have utility as diagnostic agents, research agents and agents useful in drug development and evaluation. These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain procedures, compounds and/or compositions, and are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compounds useful as corticotropin-releasing factor (CRF) receptor antagonists and as PET ligands.

In a first embodiment, the CRF receptor antagonists of this invention are taken from 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(S)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl}amino)pyrazolo[2,3-a]pyrimidine and 6-(cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-(S)-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene.

In another embodiment, the CRF antagonist is labeled with a positron emitting isotope to allow for imaging of the antagonist by PET. The isotope is generally taken from ^{11}C and ^{18}F as these isotopes may generally be added as the last step of a synthesis, may be purified quickly and may be administered to a subject, generally in intravenous form.

The compounds of the present invention may generally be utilized as the free base. Alternatively, the compounds of this invention may be used in the form of acid addition salts. Acid addition salts of the free base amino compounds of the present invention 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. Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all acceptable salt forms.

In general, the compounds of the present invention may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth in the Examples.

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 the present invention 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.*, [^{125}I]tyrosine-CFR) to its 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 IC_{50} 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)).

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 neurological 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), pain, Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).

Additional uses of the PET labeled CRF receptor antagonists of the present invention include use in clinical research and diagnosis of various disease states involving the CRF receptor. The labeled CRF receptor antagonists may also useful in the study of pharmacology, drug pharmacokinetics, pharmacodynamics, biodistribution and metabolism (Victor Pike, *Drug Information Journal*, **31** (1997), 997-1013).

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, PA 1990.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in

vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound.

In another embodiment, the present invention provides a method for treating a variety of disorders or illnesses, including endocrine, psychiatric and neurological 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, pain, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

The CRF receptor antagonists of this invention may be prepared by the methods disclosed in Examples 1 to 4. Example 5 presents a method for determining the receptor binding affinity.

Analytical HPLC-MS (LC-MS)

HP 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (electrospray);

HPLC column: YMC ODS AQ, S-5, 5μ, 2.0 x50 mm cartridge;

HPLC gradients: 1.5 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 2.5 minutes, maintaining 90 % for 1 minute.

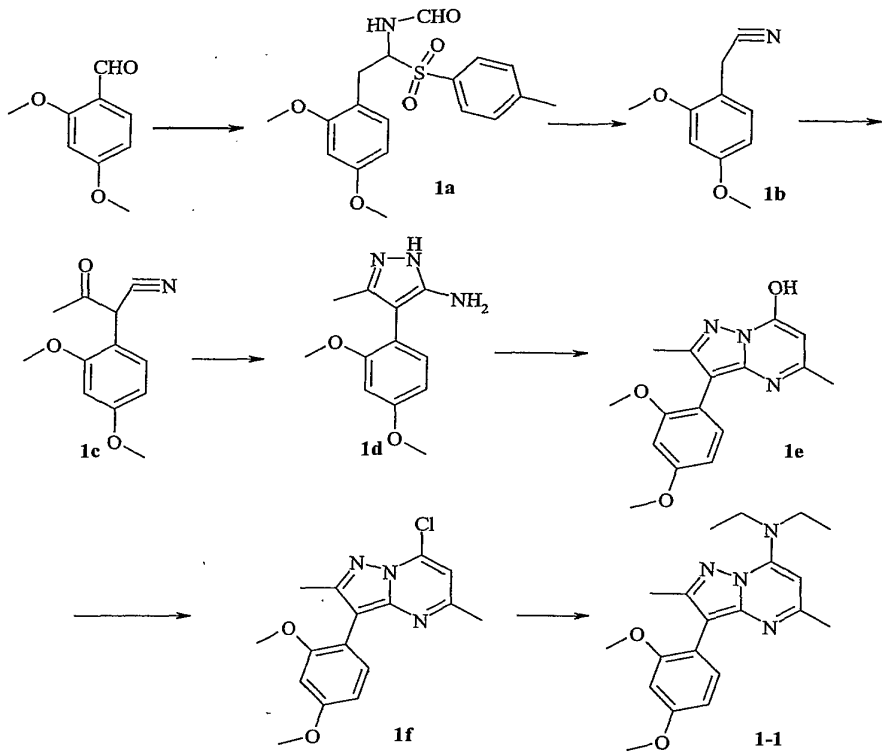
Prep. HPLC-MS

Gilson HPLC-MS equipped with Gilson 215 auto-sampler/fraction collector, an UV detector and a ThermoFinnigan AQA Single QUAD Mass detector (electrospray);

HPLC column: BHK ODS-O/B, 5 μ, 30x75 mm

HPLC gradients: 35 mL/minute, 10 % acetonitrile in water to 100 % acetonitrile in 7 minutes, maintaining 100 % acetonitrile for 3 minutes.

EXAMPLE 1



Step 1A:

A suspension of potassium t-butyloxide (7.3 g, 65 mmol, 1.4 eq) in 1,2-dimethoxyethane (DME, 40 mL) was chilled to –50 °C under nitrogen. Tosylmethyl isocyanide (9.1 g, 46.5 mmol, 1 eq) in 40 mL DME was added dropwise while the temperature was kept below –50 °C. 2,4-Dimethoxybenzaldehyde (7.7 g, 46.5 mmol, 1 eq) was added dropwise and the reaction mixture was stirred for 30 minutes to give compound **1a**. MeOH (100mL) was added and the mixture was refluxed for 30 minutes. Most of the DME and MeOH were removed, the residue was resuspended in water (100 mL) and ethyl acetate (100 mL). Following neutralization with acetic acid, the organic layer was washed with brine and dried under sodium sulfate, concentrated and purified by silica gel column using 25% ethyl acetate in hexane to yield 5.5g of **1b** as a white solid.

Step 1B:

To 2, 4-dimethoxyphenylacetonitrile **1b** (36.0 g, 204 mmol, 1 equiv.) in dry THF (300 mL) was added 12 g (510 mmol, 2.5 equiv) of 60% NaH portionwise. A few drops of EtOAc were added and the reaction was heated gently to initiate the reaction. The remaining EtOAc (150 mL) was then added dropwise. After 2 hours the reaction was poured into ice water and was washed with ether. The aqueous layer was acidified to pH = 6 and was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated in vacuo to give 44.2 g of **1c**.

Step 1C:

A mixture of **1c** (8.17 g, 37.3 mmol) and hydrazine monohydrobromide (15.3 g, 135.4 mmol) was refluxed in EtOH/H_2O (6:1) for 5 h. After evaporation of EtOH, the residue was extracted with EtOAc and water. The organic phase was dried and evaporated to dryness to give **1d**.

Step 1D:

A mixture of the compound **1d** (6.5 g, 27.9 mmol) was refluxed with ethyl acetoacetate (5.0 mL) in acetic acid (100 mL) for 3 h. After evaporation of AcOH, ethyl ether was added and **1e** (10.4 g) was obtained after filtration through a medium fritted funnel. In place of the acetic acid solvent, the reaction may be refluxed in dioxane (50 mL) overnight followed by addition of ether to precipitate the product.

Step 1E:

To a suspension of compound **1e** (1.9 g, 6.3 mmol) in acetonitrile was added $POCl_3$ (2.2 mL, 24.1 mmol). The suspension was heat to reflux for 5 h. The resulting orange solution was cooled to room temperature and poured onto ice-water. After extraction with EtOAc, compound **1f** was obtained by column chromatography purification (1.70 g, 85%).

Step 1F:

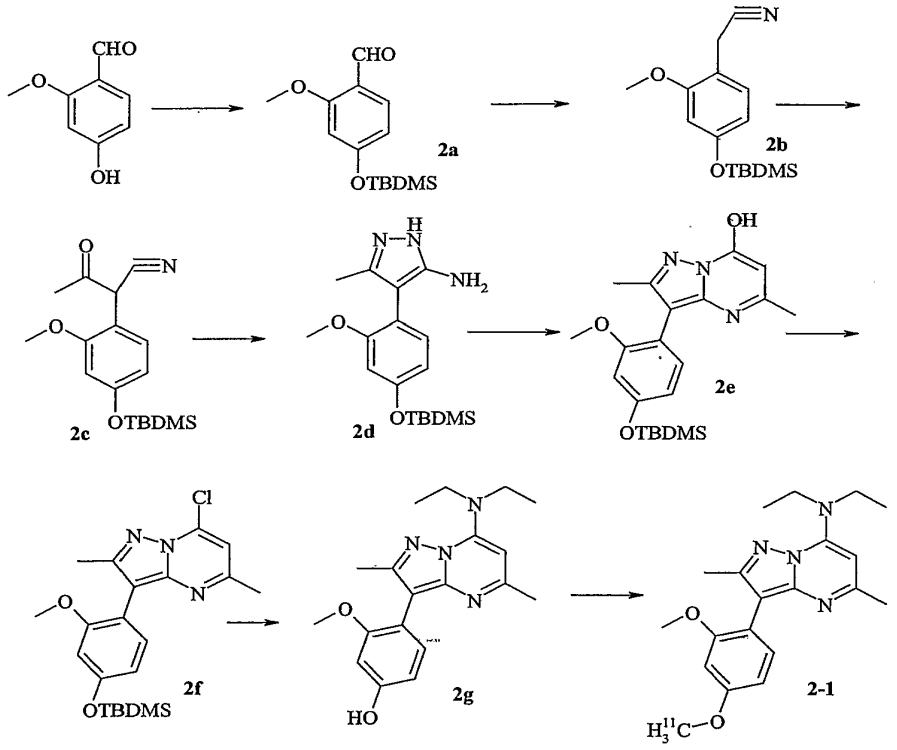
Compound **1f** (30 mg) and excess diethylamine in acetonitrile (0.8 mL) were heated at 160 °C with a microwave for 16 min. Purification with a Sciex2 prep LC-MS system

gave 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine **1-1**. LCMS 355 (MH^+), FW = 354.45

Following the same general procedure the following compounds were also synthesized: 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine. LCMS 385 (MH^+), FW = 384.48;

2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(S)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine. LCMS 396 (MH^+), FW = 396.49.

EXAMPLE 2

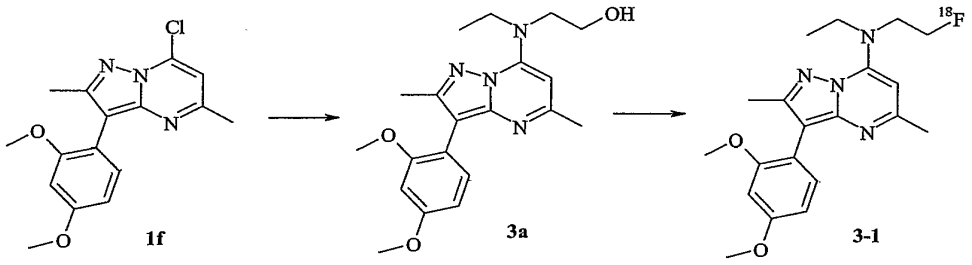


Step 2A:

2-Hydroxy-4-methoxybenzaldehyde is protected by reaction with tert-butyldimethylsilyl chloride (TBDMSCl) and imidazole in DMF to give the tert-

butyldimethylsilyl ether **2a**. Using **2a** and following the procedure as outlined in steps 1A to 1E, compound **2f** is realized. **2f** and diethylamine following the procedure of Step 1F followed by deprotection of the tert-butyldimethylsilyl group with tetrabutylammonium fluoride or acid under standard conditions gives **2g**. Alkylation of the hydroxy group of **2g** with ^{11}C methyl iodide and sodium hydride in solvent such as DMF or acetonitrile gives **2-1**.

EXAMPLE 3



Step 3A:

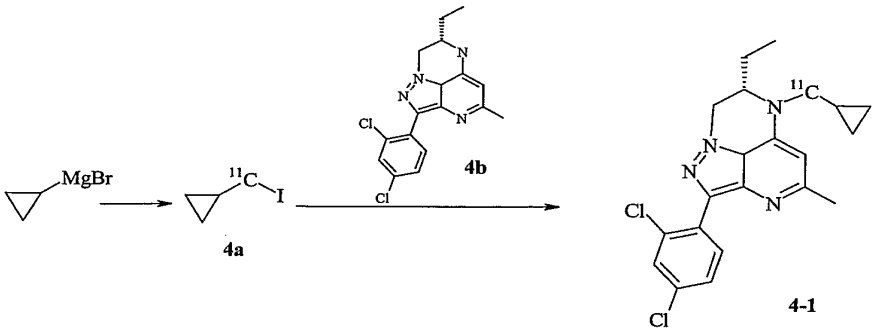
Compound **1f** and ethylaminoethanol following the procedure of Step 1F gives **3a**.

Step 3B:

Compound **3a** is converted to the sulfonate ester such as mesylate, tosylate or triflate followed by reaction with ^{18}F ion to give **3-1** (L. Martarello et al., Nuclear Medicine and Biology **28** (2001) 187-195). Compound **3a** and methanesulfonyl chloride in pyridine yields a mesylate which undergoes a nucleophilic substitution with $K^{18}F$ to give **3-1** which is purified by HPLC.

EXAMPLE 4

6-(CYCLOPROPYLMETHYL)-2-(2,4-DICHLOROPHENYL)-7-(S)-ETHYL-7,8-DIHYDRO-4-METHYL-6H-1,3,6,8A-TETRAAZAACENAPHTHYLENE



Step 4A:

According to the general procedure of Ishiwata et al., *Appl. Radiat. Isot.*, **46**, 10: 1009-1013, cyclopropyl-[^{11}C]-methyliodide is prepared. [^{11}C]CO_2 is transferred into a solution of cyclopropyl magnesium bromide in THF at 0 – 5 °C, followed by immediate reduction with lithium aluminum hydride. Hydroiodic acid is added, the mixture is heated to give **4a** after purification.

Step 4B:

Compound **4b** (synthesized according to various procedures in U.S. Patent No. 6,531,475) is alkylated with compound **4a** using standard conditions such as sodium hydride, sodium methoxide or cesium carbonate in a solvent such as DMF followed by purification by HPLC to give **4-1**.

EXAMPLE 5

CRF RECEPTOR BINDING ACTIVITY

The compounds of this invention may be evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by

Grigoriadis et al. (*Mol. Pharmacol* vol50, pp679-686, 1996) and Hoare et al. (*Mol. Pharmacol* vol63 pp751-765, 2003.) By utilizing radiolabeled CRF ligands, the assay may be used to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype.

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

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.

CLAIMS

1. A compound taken from 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(S)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, and 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl}amino)pyrazolo[2,3-a]pyrimidine.
2. A compound taken from 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(diethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-methoxyethylamino)pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-{2-(S)-methoxymethylpyrrolidinyl}-pyrazolo[2,3-a]pyrimidine, 2,5-dimethyl-3-(2,4-dimethoxyphenyl)-7-(*N*-ethyl-*N*-{2-fluoroethyl}amino)pyrazolo[2,3-a]pyrimidine and 6-(cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-(S)-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene for use as PET ligands.
3. A composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent.
4. A method for treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal comprising administering to the animal an effective amount of the pharmaceutical composition of claim 3.
5. The method of claim 4 wherein the disorder is depression.
6. The method of claim 4 wherein the disorder is an anxiety-related disorder.
7. The method of claim 4 wherein the disorder is irritable bowel syndrome.
8. A composition comprising a compound of claim 2 in combination with a pharmaceutically acceptable carrier or diluent.

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(71) Applicants *(for all designated States except US)*: **SB PHARMCO PUERTO RICO INC** [US/US]; The Prentice Hall Corp System of PR Inc, c/o FGR Corporate Services Inc, BBV Tower 8th Floor, 254 Munoz Rivera Avenue, San Juan, Puerto Rico 00918 (US). **NEUROCRINE BIOSCIENCES INC** [US/US]; 12790 El Camino Real, San Diego, California 92130 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LUO, Zhiyong** [CN/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, California 92130 (US). **SLEE, Deborah** [US/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, California 92130 (US). **TELLEW, John, Edward** [US/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, CA 92130 (US). **WILLIAMS, John** [US/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, CA 92130 (US). **ZHANG, Xiahou** [CN/US]; Neurocrine Biosciences Inc, 12790 El Camino Real, San Diego, CA 92130 (US).

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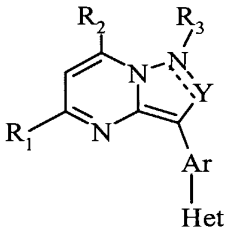
(54) Title: CRF RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO



(I)

(57) Abstract: CRF receptor antagonists are disclosed which have utility in the treatment of a variety of disorders, including the treatment of disorders manifesting hypersecretion of CRF in a warm-blooded animals, such as stroke. The CRF receptor antagonists of this invention have the following structure (I), including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof, wherein R1, R2, R3, Y, Ar, and Het are as defined herein. Compositions containing a CRF receptor antagonist in combination with a pharmaceutically acceptable carrier are also disclosed, as well as methods for use of the same.

CRF RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application Serial No. 60/532,031, filed December 12, 2003, the entire disclosure of which is incorporated by reference herein.

FIELD OF THE INVENTION

This invention relates generally to CRF receptor antagonists and to methods of treating disorders by administration of such antagonists to a mammal in need thereof.

BACKGROUND OF THE INVENTION

The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalami 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).

CRF has been found to produce profound alterations in endocrine, nervous and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotropic hormone ("ACTH"), ß-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 effects by binding to a plasma membrane receptor which has been found to be distributed throughout the brain (DeSouza et al., *Science 224*: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). The receptor for CRF has now been cloned from rat (Perrin et al., *Endo 133*(6):3058-3061, 1993), and human brain (Chen et al., *PNAS 90*(19):8967-8971, 1993; Vita et al., *FEBS 335*(1):1-5, 1993). This receptor is a 415 amino acid protein comprising seven membrane spanning domains. A comparison of identity

between rat and human sequences shows a high degree of homology (97%) at the amino acid level.

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 system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.

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. 278*:332, 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 suggests 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 suggests 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.

The first CRF receptor antagonists were peptides (*see, e.g.*, Rivier et al., U.S. Patent No. 4,605,642; Rivier et al., *Science 224*:889, 1984). While these peptides established that CRF receptor antagonists can attenuate the pharmacological responses to CRF, peptide CRF receptor antagonists suffer from the usual drawbacks of peptide therapeutics including lack of stability and limited oral activity. Some published patent documents include US6313124, WO 01/23388, and WO 97/29109, all of which disclose pyrazolopyrimidine compounds as CRF antagonists. Published

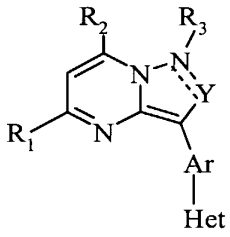
application WO 98/54093 described certain pyrazolopyrimidine compounds as tyrosine kinase inhibitors.

Due to the physiological significance of CRF, the development of 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 neurological conditions or illnesses, including stress-related disorders in general.

While significant strides have been made toward achieving CRF regulation through administration of CRF receptor antagonists, there remains a need in the art for effective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as methods relating to the use thereof to treat, for example, stress-related disorders. The present invention fulfills these needs, and provides other related advantages.

SUMMARY OF THE INVENTION

In brief, this invention is generally directed to CRF receptor antagonists, and more specifically to CRF receptor antagonists having the following general structure (I):



(I)

and pharmaceutically acceptable salts, esters, solvates, stereoisomers and prodrugs thereof, wherein R_1, R_2, R_3, Y, Ar, and Het are as defined below.

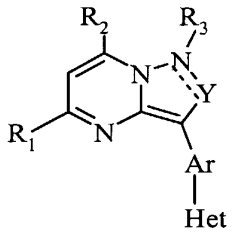
The CRF receptor antagonists of this invention may have utility over a wide range of therapeutic applications, and may be used to treat a variety of disorders or illnesses, including stress-related disorders. Such methods include administering a pharmaceutically effective amount of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition, to an animal in need thereof. Accordingly, in another embodiment, pharmaceutical compositions are disclosed containing one or more CRF receptor antagonists of this invention and a pharmaceutically acceptable carrier and/or diluent.

These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain procedures, compounds and/or compositions, and are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to corticotropin-releasing factor (CRF) receptor antagonists.

In a first embodiment, the CRF receptor antagonists of this invention have the following structure (I):



(I)

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

wherein:

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

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

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

R_3 is null, hydrogen, or alkyl;

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

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

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

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

Het is heteroaryl optionally substituted with 1 or 2 R_6;

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

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

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

As used herein, the above terms have the following meaning:

"Alkyl" means a straight chain or branched, acyclic or cyclic, unsaturated or saturated hydrocarbon containing from 1 to 10 carbon atoms, while the term "lower alkyl" has the same meaning as alkyl but contains from 1 to 6 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, -CH_2-cyclopentyl, -CH_2-cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like. Cyclic alkyls, also referred to as "homocyclic rings," and include di- and poly-homocyclic rings such as decalin and adamantyl. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an "alkenyl" or "alkynyl", respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1 butynyl, and the like.

"Alkylidenyl" represents a divalent alkyl from which two hydrogen atoms are taken from the same carbon atom, such as =CH_2, =$CHCH_3$, =$CHCH_2CH_3$, =$C(CH_3)CH_2CH_3$, and the like.

"Aryl" means an aromatic carbocyclic moiety such as phenyl or naphthyl.

"Arylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with an aryl, such as benzyl (*i.e.,* -CH_2-phenyl), -CH_2-(1- or 2-naphthyl), -$(CH_2)_2$-phenyl, -$(CH_2)_3$-phenyl, -$CH(phenyl)_2$, and the like.

"Aryloxyalkyl" means an aryl attached through an oxygen bridge to an alkyl (*i.e.,* aryl-O-alkyl-) such as -methyl-O-phenyl, and such.

"Heteroaryl" means an aromatic heterocycle ring of 5- to 10-members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems. Representative heteroaryls include (but are not limited to) furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"Heteroarylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl, such as -CH_2-pyridinyl, -CH_2-pyrimidinyl, and the like.

"Heterocycle" (also referred to herein as a "heterocycle ring") means a 5- to 7-membered monocyclic, or 7- to 14-membered polycyclic, heterocycle ring which is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring as well as tricyclic (and higher) heterocyclic rings. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Thus, in addition to the aromatic heteroaryls listed above, heterocycles also include (but are not limited to) morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperizinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocyclealkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heterocycle, such as -CH_2-morpholinyl, and the like.

The term "substituted" as used herein refers to any group (*e.g.,* alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle or heterocyclealkyl) wherein at least one hydrogen atom is replaced with a substituent. In the case of a keto substituent ("-C(=O)-") two hydrogen atoms are replaced. "Substituents" within the context of this invention include halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, alkyl, alkoxy, thioalkyl, haloalkyl, hydroxyalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, -NR_aR_b, -$NR_aC(=O)R_b$, -$NR_aC(=O)NR_aR_b$, -$NR_aC(=O)OR_b$ -$NR_aSO_2R_b$, -OR_a, -$C(=O)R_a$ -$C(=O)OR_a$, -$C(=O)NR_aR_b$, -$OC(=O)NR_aR_b$, -SH, -SR_a,

$-SOR_a$, $-S(=O)_2R_a$, $-OS(=O)_2R_a$, $-S(=O)_2OR_a$, wherein R_a and R_b are the same or different and independently hydrogen, alkyl, haloalkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl.

"Halogen" means fluoro, chloro, bromo or iodo.

"Haloalkyl" means an alkyl having at least one hydrogen atom replaced with halogen, such as trifluoromethyl and the like. Haloalkyl is a specific embodiment of substituted alkyl, wherein alkyl is substituted with one or more halogen atoms.

"Alkoxy" means an alkyl attached through an oxygen bridge (*i.e.,* -O-alkyl) such as –O-methyl, -O-ethyl, and the like.

"Thioalkyl" means an alkyl attached through a sulfur bridge (*i.e.,* -S-alkyl) such as –S-methyl, -S-ethyl, and the like.

"Alkylamino" and "dialkylamino" mean one or two alkyl moieties attached through a nitrogen bridge (*i.e.,* -NHalkyl or –N(alkyl)(alkyl)) such as methylamino, ethylamino, dimethylamino, diethylamino, and the like.

"Hydroxyalkyl" means an alkyl substituted with at least one hydroxy group.

"Mono- or di(cycloalkyl)methyl" represents a methyl group substituted with one or two cycloalkyl groups, such as cyclopropylmethyl, dicyclopropylmethyl, and the like.

"Alkylcarbonylalkyl" represents an alkyl substituted with a -C(=O)alkyl group.

"Alkylcarbonyloxyalkyl" represents an alkyl substituted with a -C(=O)Oalkyl group or a -OC(=O)alkyl group.

"Alkoxyalkyl" represents an alkyl substituted with a -O-alkyl group.

"Alkylthioalkyl" represents a alkyl substituted with a -S-alkyl group.

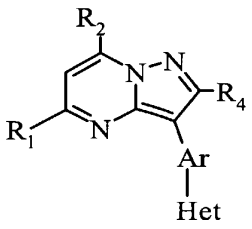
"Mono- or di(alkyl)amino represents an amino substituted with one alkyl or with two alkyls, respectively.

"Mono- or di(alkyl)aminoalkyl" represents an alkyl substituted with a mono- or di(alkyl)amino.

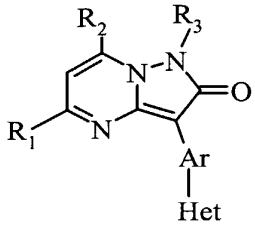
"Alkylsulfonyl or alkylsulfinyl" represents an alkyl substituted with a ($-S(=O)_2-$) or (-S(=O)-) functionality, respectively.

Embodiments of this invention presented herein are for purposes of example and not for purposes of limitation. In a first embodiment of the invention, R_3 is

null and Y is =(CR_4)- in the following structure (II), and in a further embodiment Y is -(C=O)- in the following structure (III).

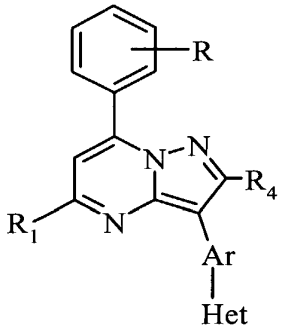


(II)



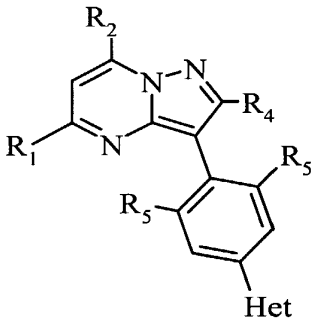
(III)

Further embodiments of this invention have structure (IV) when R_2 is phenyl, R is an optional substituent of said phenyl, and Y is =(CR_4)-.

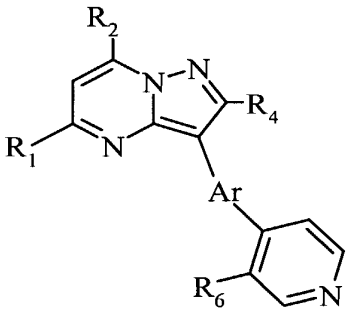


(IV)

In further embodiments of this invention wherein Y is =(CR_4)-, Ar is phenyl substituted with 2 R_5 in structure (V) and Het is pyridyl substituted with 1 R_6 in structure (IV).



(V)



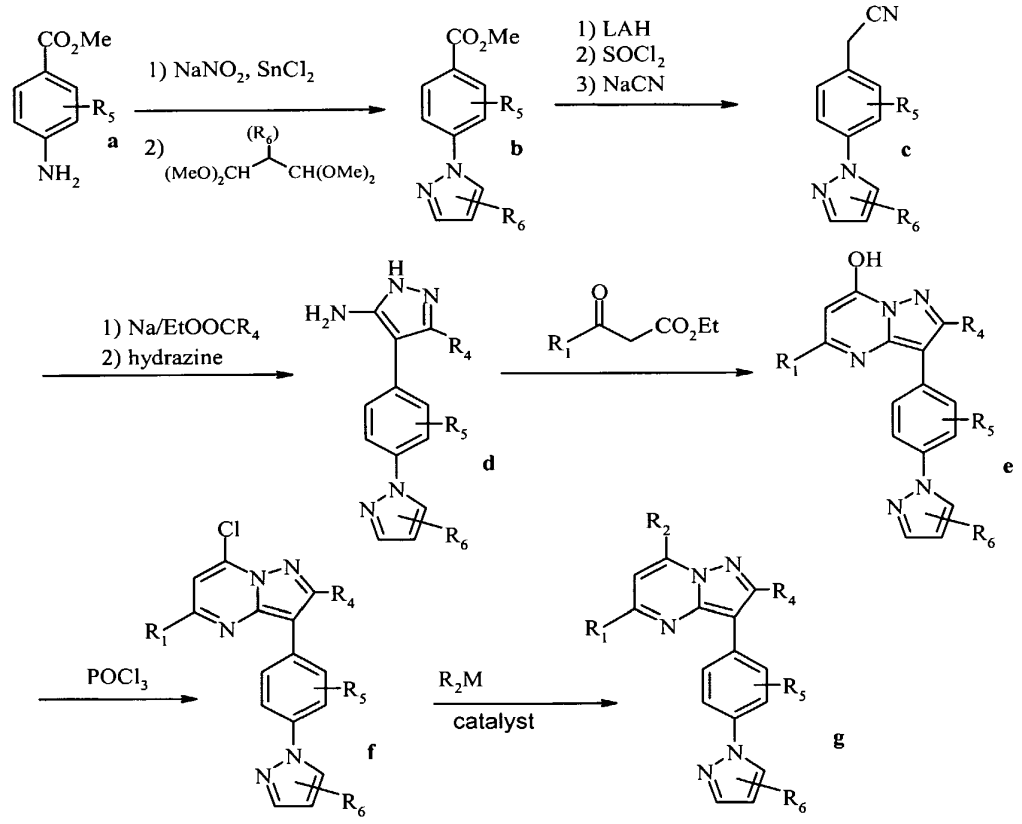
(VI)

The compounds of the present invention may generally be utilized as the free base. Alternatively, the compounds of this invention may be used in the form

of acid addition salts. Acid addition salts of the free base amino compounds of the present invention 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. Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all pharmaceutically acceptable salt forms.

In general, the compounds of structure (I) may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth in the Examples. Examples of synthetic procedures which may be used to prepare compounds according to the invention are illustrated in Reaction Schemes 1-3.

Reaction Scheme 1

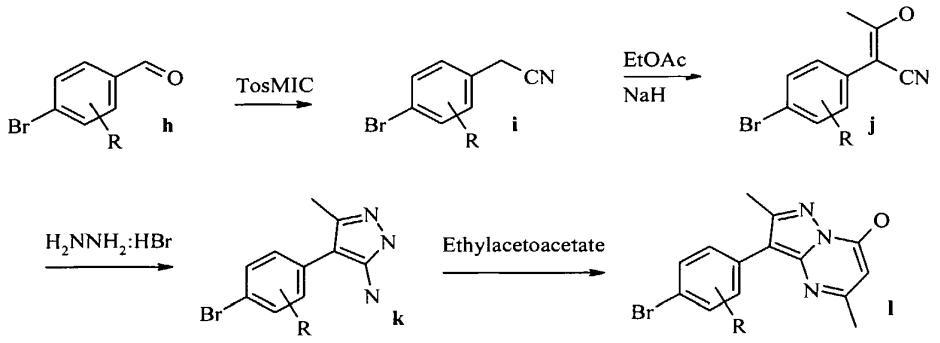


The amino functionality of 4-aminobenzoate **a** may be condensed with an, optionally, substituted malonaldehyde to give the corresponding 4-pyrazol-1-yl benzoate **b**. After reaction with LAH, $SOCl_2$, and NaCN to give conversion to the pyrazolophenylacetonitrile compound **c**, reaction with Na/ethyl carboxylic acid ester and hydrazine yields the bis-pyrazole **d**. Reaction with the appropriately substituted β-keto ester gives pyrazolopyrimidine **e** which reacts with $POCl_3$ to give the chloride **f**. Reaction of the chloride **f** with an appropriate organometallic reagent R_2M in the presence of a suitable catalyst or promoter gives compound **g**. Examples of suitable organometallic reagents and suitable catalysts/promoters include:

1. (substituted) alkyl grignard reagents R_2MgX ($Fe(acac)_3$ promoter);
2. aryl, heteroaryl, or alkenyl boronic acids or esters ($Pd(PhP)_4$ catalyst); and
3. aryl or heteroaryl zinc reagents ($Pd(PhP)_4$ catalyst).

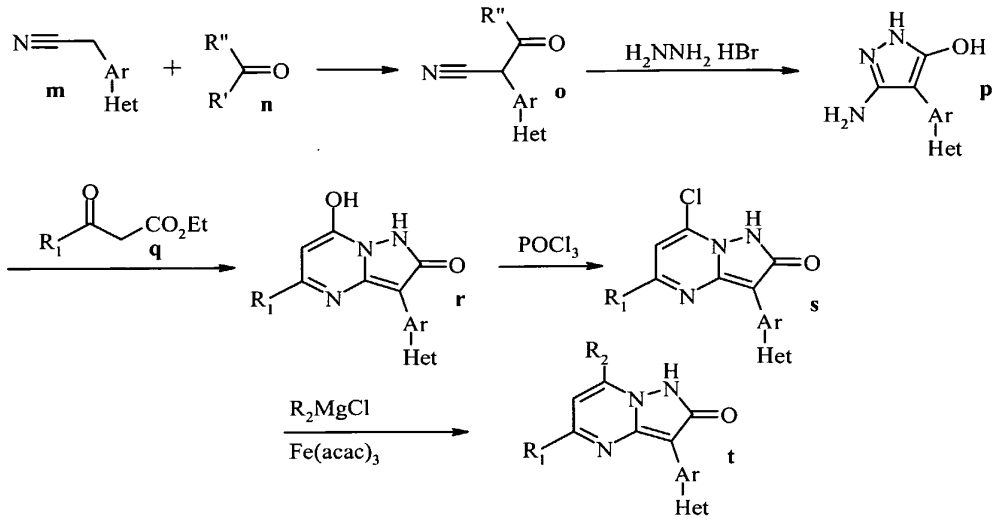
The R_2 groups thus installed may be further manipulated or reacted, using standard methods known to those skilled in the art (for example oxidation/reduction, hydrolysis, and the like), to provide further examples of the invention.

Reaction Scheme 2



Multiple synthetic routes to the pyrazolopyrimidine core of the invention are available. In Reaction Scheme 2, the optionally substituted halobenzaldehyde **h** reacts with tosylmethyl isocyanide (TosMIC) to form the phenylacetonitrile **i**. Reaction of **i** with NaH and EtOAc gives the 3-hydroxy but-2-enenitrile **j** which undergoes ring closure in reaction with hydrazine HBr to give the 3-amino 2-phenyl pyrazole **k**. Addition of the β-keto ester gives the pyrazolo[1,5-a]pyrimidin-7-ol **l**. Substitution of the oxygen as in Reaction Scheme 1 and substitution of the distal bromine with Het gives compounds according to the invention.

Reaction Scheme 3



Reaction of substituted acetonitrile **m** with ketone **n**, where R' is a good leaving group such as alkoxy, cyano, or halo and where R" is a group such as hydroxy or alkoxy gives cyanoketone **o** which reacts with hydrazine to give substituted pyrazole **p**. Reaction of **p** with β-keto ester **q** gives pyrazolopyrimidine **r**. Reaction with $POCl_3$ gives the chloride **s**, and substitution of chloride by R_2 gives compound **t**.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention may be 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.*, [^{125}I]tyrosine-CFR) to its 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 IC_{50} 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 1μM, and more preferably less than 0.25 μM (*i.e.,* 250 nM). As set forth in greater detail below, the K_i values may be assayed by the methods set forth in Example 27.

CRF receptor antagonists of the present invention may 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 neurological disorders or illnesses. More specifically, 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, CRF receptor antagonists of the present invention may be used to treat neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by 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 CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), pain, 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, PA 1990.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound.

With regard to stereoisomers, the compounds of structure (I) may have chiral centers and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present

invention, including mixtures thereof. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist in alternative crystalline, amorphous or polymorphic forms as polymorphs, all of which are included in the present invention. In addition, some of the compounds of structure (I) may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of this invention.

In another embodiment, the present invention provides a method for treating a variety of disorders or illnesses, including endocrine, psychiatric and neurological 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 may 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.

In another embodiment, the present invention permits the diagnostic visualization of specific sites within the body by the use of radioactive or non-radioactive pharmaceutical agents. Use of a compound of the present invention may provide a physiological, functional, or biological assessment of a patient or provide disease or pathology detection and assessment. Radioactive pharmaceuticals are employed in scintigraphy, positron emission tomography (PET), computerized tomography (CT), and single photon emission computerized tomography (SPECT.) For such applications, radioisotopes are incorporated of such elements as iodine (I) including ^{123}I (PET), ^{125}I (SPECT), and ^{131}I, technetium (Tc) including ^{99}Tc (PET), phosphorus (P) including ^{31}P and ^{32}P, chromium (Cr) including ^{51}Cr, carbon (C) including ^{11}C, fluorine (F) including ^{18}F, thallium (Tl) including ^{201}Tl, and like emitters of positron and ionizing radiation. Non-radioactive pharmaceuticals are employed in magnetic resonance imaging (MRI), fluoroscopy, and ultrasound. For such applications, isotopes are incorporated of such elements as gadolinium (Gd) including ^{153}Gd, iron (Fe), barium (Ba), manganese (Mn), and thallium (Tl). Such entities are

also useful for identifying the presence of particular target sites in a mixture and for labeling molecules in a mixture.

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, 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, pain, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

The CRF receptor antagonists of this invention may be prepared by the methods disclosed in Examples 1 to 26. Example 27 presents a method for determining the receptor binding affinity, and Example 28 discloses an assay for screening compounds of this invention for CRF-stimulated adenylate cyclase activity.

Analytical HPLC-MS Method 1

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI);

HPLC column: YMC ODS AQ, S-5, 5µ, 2.0 x50 mm cartridge;

HPLC gradient: 1.0 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 2.5 minutes, maintaining 90 % for 1 minute. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 2

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI);

HPLC column: Phenomenex Synergi-Max RP, 2.0 x 50 mm column;

HPLC gradient: 1.0 mL/minute, from 5 % acetonitrile in water to 95 % acetonitrile in water in 13.5 minutes, maintaining 95 % for 2 minute. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 3

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (electrospray);

HPLC column: XTerra MS, C_{18}, 5µ, 3.0 x 250 mm column;

HPLC gradient: 1.0 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 46 minutes, jump to 99% acetonitrile and maintain 99 % acetonitrile for 8.04 minutes. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 4

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI) and Berger FCM 1200 CO_2 pump module;

HPLC column: Berger Pyridine, PYR 60A, 6µ, 4.6 x 150 mm column;

HPLC gradient: 4.0 mL/minute, 120 bar; from 10 % methanol in supercritical CO_2 to 60% methanol in supercritical CO_2 in 1.67 minutes, maintaining 60 % for 1 minute. Methanol has 1.5% water. Backpressure regulated at 140 bar.

Preparative HPLC-MS

Platform: Shimadzu HPLC equipped with a Gilson 215 auto-sampler/fraction collector, UV detector and a PE Sciez API150EX mass detector;

HPLC column: BHK ODS-O/B, 5 µ, 30x75 mm

HPLC gradient: 35 mL/minute, 10% acetonitrile in water to 100 % acetonitrile in 7 minutes, maintaining 100 % acetonitrile for 3 minutes, with 0.025% TFA.

Abbreviations:

AA: Acetyl acetate

LAH: Lithium aluminum hydride

DCM: Dichloromethane

DMSO: Dimethyl sulfoxide

EAA: Ethyl acetoacetate

LC-MS: liquid chromatography-mass spectroscopy

$NaBH(OAc)_3$: Sodium Triacetoxyborohydride

Pd-C: Palladium (10 %) on Carbon

TFA: Trifluoroacetic acid

Tosmic: Tosylmethyl isocyanide

acac: acetylacetonate

EDCI: N-ethyl-N'-(dimethylaminopropyl)carbodiimide hydrochloride

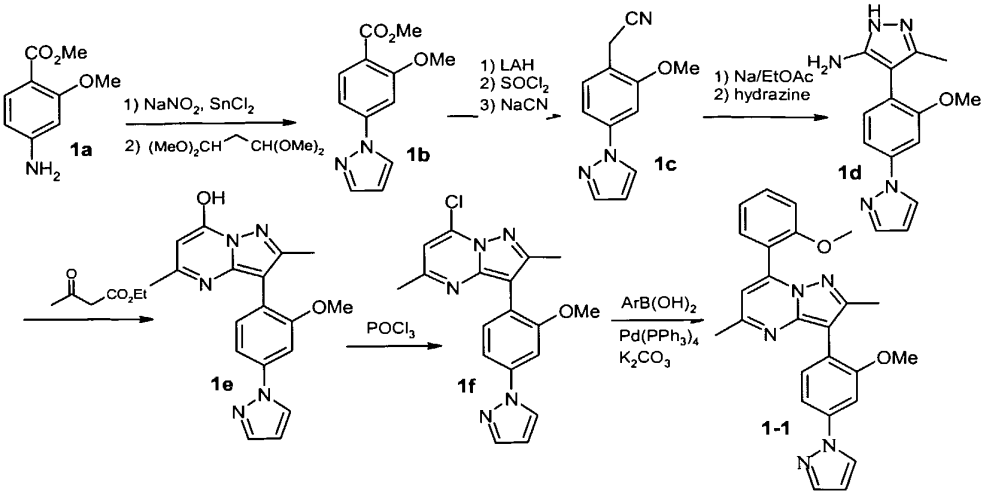
THF: tetrahydrofuran

TEA: triethylamine

t_R: Retention time

EXAMPLE 1

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



Step 1A:

To a cooled suspension of methyl 4-amino-2-methoxybenzoate (6.82 g, 37.7 mmol) in 6N HCl (aqueous) was added a solution of sodium nitrite (2.60 g, 37.7 mmol) dropwise. After stirring at 0 °C for 20 min, stannous chloride dihydrate (24.7 g, 109.3 mmol) was added portionwise. The resulting suspension was stirred at 0 °C for 1.5 hr prior to filtration. The collected solid was suspended in EtOH to which malonaldehyde bis(dimethyl acetal) (7.5 mL, 45.7 mmol) was added, and this reaction mixture was subjected to reflux overnight. After evaporation of EtOH, the residue was extracted between EtOAc and water, and the organic phase was dried and evaporated to dryness. The residue was passed through a silica gel plug (25% EtOAc/hexane) to yield Cmpd **1b** (7.43 g) as a mixture of the methyl and ethyl benzoate.

Step 1B:

To a solution of **1b** (10.6 g) in dry diethyl ether (200 mL) was added LAH powder (1.74 g) slowly at 0 °C. After stirring for 45 min at 0 °C the reaction mixture was decanted onto ice-water, and the aqueous phase was acidified to pH 4.0. After isolation, the alcohol (8.8 g) was refluxed with thionyl chloride (10 mL) in DCM for 2.5 hr, decanted onto ice-water, and extracted with DCM. The crude benzyl chloride (8.26 g) was heated with NaCN (3.65 g, 74.4 mmol) in DMSO (100 mL) at 80 °C for 45 min. After removal of DMSO, Cmpd **1c** (5.98 g) obtained after column chromatography with 30% EtOAc/hexane.

Step 1C:

To a solution of **1c** (5.98 g, 28.1 mmol) in EtOAc (150 mL) was added metallic sodium (1.0 g, 43.5 mmol) portionwise, and the mixture was refluxed overnight. The resulting suspension was decanted onto ice-water and acidified to pH 4.0. The organic phase was dried and evaporated to dryness. The resulting compound (9.5 g) was mixed with hydrazine monohydrobromide (15.3 g, 135.4 mmol,) and refluxed in EtOH/H_2O (6:1) for 5 hr. After evaporation of EtOH and extraction with EtOAc, the organic phase was dried and evaporated to dryness to yield Cmpd **1d** (7.5 g.)

Step 1D:

A mixture of **1d** (7.5 g, 27.9 mmol) was refluxed with ethyl acetoacetate (5.0 mL) in AcOH (100 mL) for 3 hr. After evaporation of AcOH and precipitation in diethyl ether, Cmpd **1e** (10.4 g) obtained after filtration.

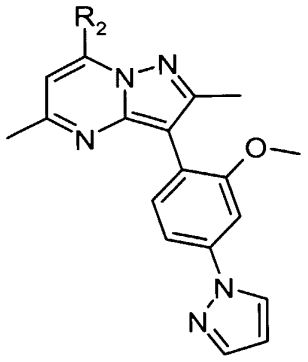
Step 1E:

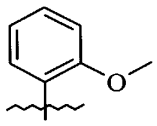
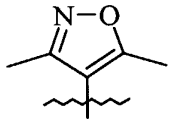
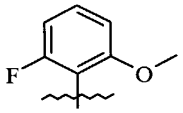
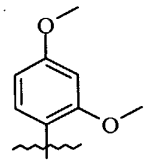
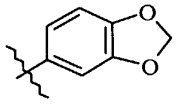
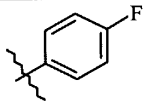
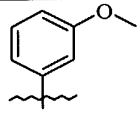
To a suspension of **1e** (2.1 g, 6.3 mmol) in acetonitrile was added $POCl_3$ (2.2 mL, 24.1 mmol,) and this mixture was refluxed for 5 hr, decanted to ice-water, and extracted with EtOAc to yield Cmpd **1f** (1.88 g) after chromatographic purification.

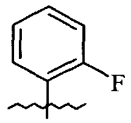
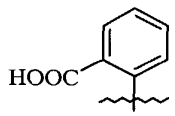
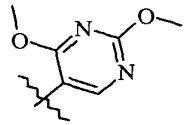
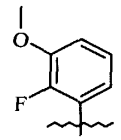
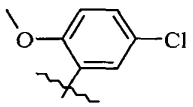
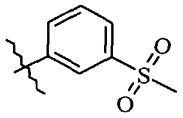
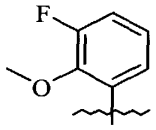
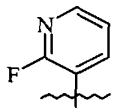
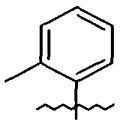
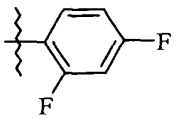
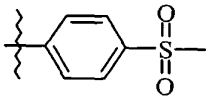
Step 1F:

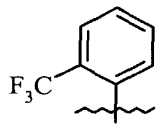
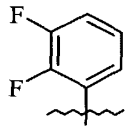
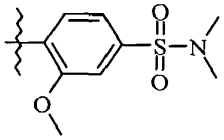
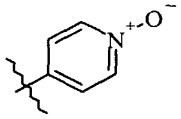
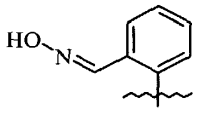
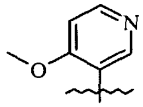
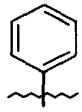
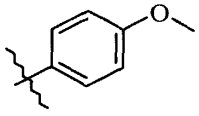
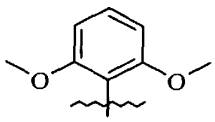
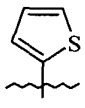
A mixture of Cmpd **1f** (1.0 mmol), 2-methoxyphenylboronic acid (1.2 mmol), K_2CO_3 (2.0 mmol) and $Pd(PPh_3)_4$ (0.05 mmol) was heated in 1,4-dioxane/H_2O (2:1) at 110 °C overnight. After evaporation of solvent, the mixture was extracted between $CHCl_3$/H_2O, and the organic phase was dried and evaporated to dryness. Cmpd **1-1** (402 mg) was obtained after column chromatography. Depending on the

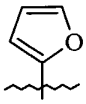
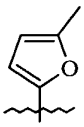
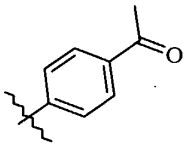
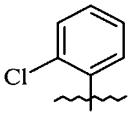
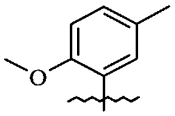
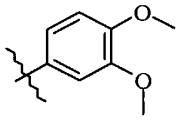
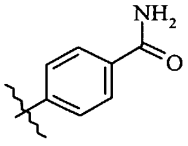
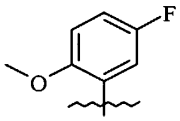
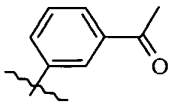
aryl functionality in the arylboronic acid reagent, the compounds listed in the following table were synthesized and purified by preparative LC-MS:

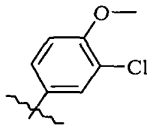
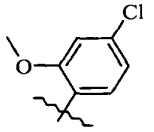
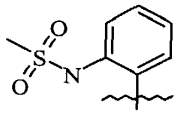
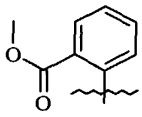
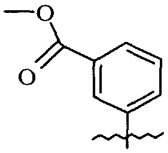
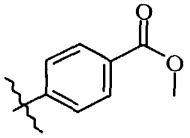
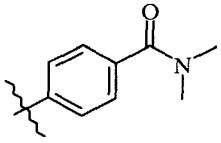
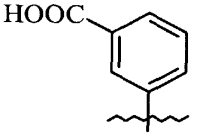
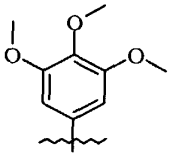
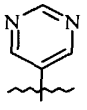


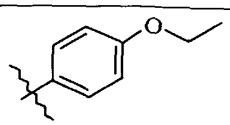
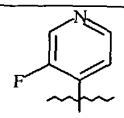
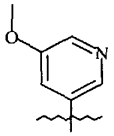
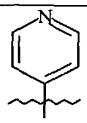
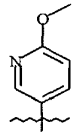
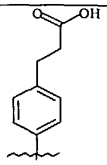
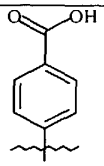
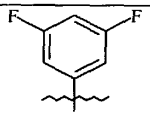
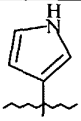
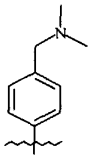
Cmpd	R_2	MW	MS	t_R	HPLC Method
1-1		425.49	425	1.315	4
1-2		414.47	414	1.586	4
1-3		443.48	443	1.335	4
1-4		455.52	455	1.32	4
1-5		439.47	439	1.353	4
1-6		413.45	413	1.25	4
1-7		425.49	425	1.317	4

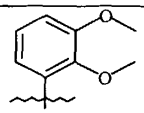
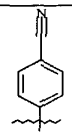
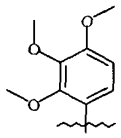
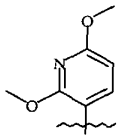
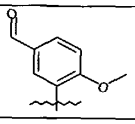
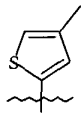
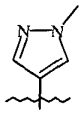
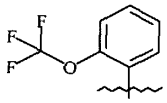
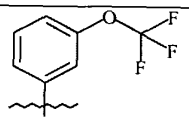
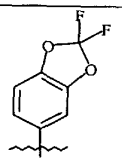
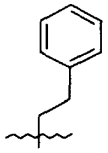
Cmpd	R_2	MW	MS	t_R	HPLC Method
1-8		413.45	413	1.236	4
1-9		439.47	439	5.625	2
1-10		457.49	457	7.09	2
1-11		443.48	443	1.226	4
1-12		459.94	459	1.188	4
1-13		473.56	473	1.446	4
1-14		443.48	443	1.120	4
1-15		414.44	414	1.242	4
1-16		409.49	409	1.088	4
1-17		431.44	431	1.071	4
1-18		473.56	473	1.514	4

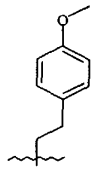
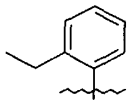
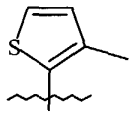
Cmpd	R_2	MW	MS	t_R	HPLC Method
1-19		463.46	463	1.030	4
1-20		431.44	431	1.165	4
1-21		502.60	502	1.469	4
1-22		412.45	412	1.506	4
1-23		438.49	438	6.463	2
1-24		426.48	426	4.405	2
1-25		395.46	396	8.240	2
1-26		425.49	425.9	8.260	2
1-27		455.52	456	7.550	2
1-28		401.49	401.9	8.490	2

Cmpd	R_2	MW	MS	t_R	HPLC Method
1-29		401.49	401.9	8.530	2
1-30		385.42	385.9	8.410	2
1-31		399.45	335.9	4.700	2
1-32		385.42	385.9	8.300	2
1-33		437.50	437	7.861	2
1-34		429.912	429	8.229	2
1-35		439.512	439	8.320	2
1-36		455.52	455	7.718	2
1-37		438.49	438	6.153	2
1-38		443.48	443	1.218	4
1-39		437.50	437	7.807	2

Cmpd	R_2	MW	MS	t_R	HPLC Method
1-40		459.94	459	8.956	2
1-41		459.94	459	8.598	2
1-42		488.57	488	7.216	2
1-43		453.50	454	7.601	2
1-44		453.50	454	8.310	2
1-45		453.50	454	8.380	2
1-46		466.54	467	6.690	2
1-47		439.47	440	7.010	2
1-48		485.54	486	8.000	2
1-49		397.44	398	6.270	2

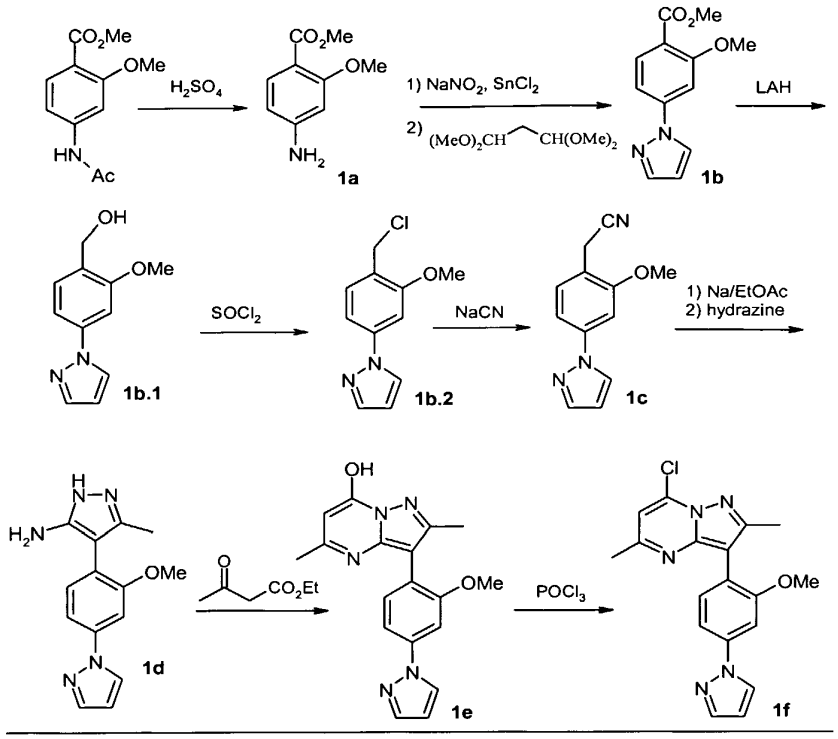
Cmpd	R_2	MW	MS	t_R	HPLC Method
1-50		439.52	439	8.288	2
1-51		414.44	414	5.640	2
1-52		426.48	426	5.910	2
1-53		396.45	396	4.920	2
1-54		426.48	426	6.630	2
1-55		467.53	468	6.970	2
1-56		439.47	440	6.710	2
1-57		431.44	432	8.660	2
1-58[1]		384.44	385	5.390	2
1-59		452.56	453	4.590	2

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:

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 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:

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. 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 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 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 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 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 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.

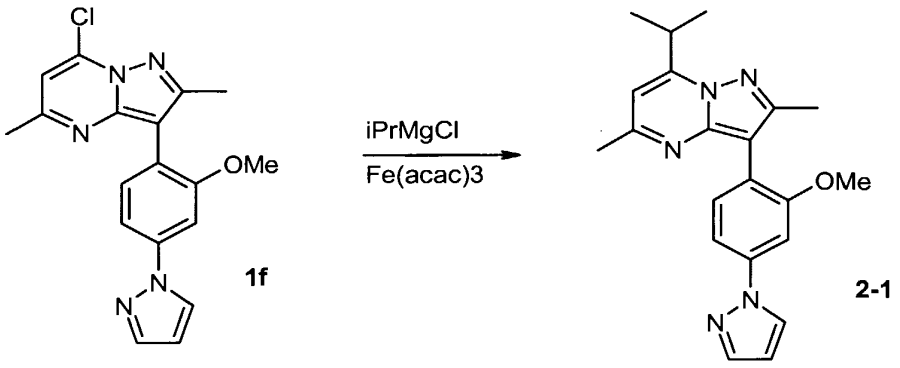
The mother liquor was concentrated, then chromatographed on silica gel using 10% methanol in DCM as eluent. The solid product thus obtained was washed with ether to provide an additional 17.0 g of **1e** as an off-white solid (combined yield 69 g).

Step 1A-H:

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, eluting with 3:1 hexanes/ethyl acetate, to yield **1f** (29.0 g) as a tan solid.

EXAMPLE 2

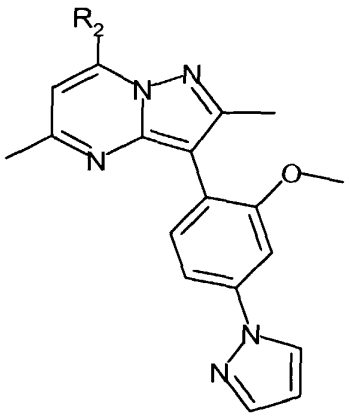
7-ISOPROPYL-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

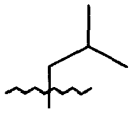
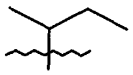
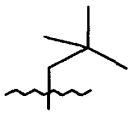
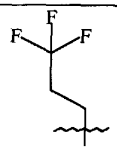
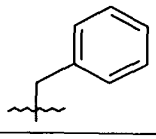


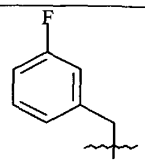
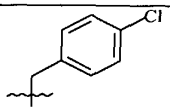
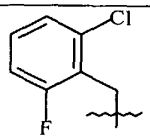
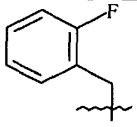
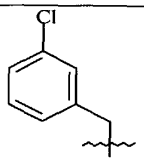
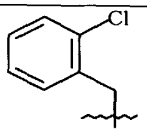
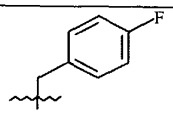
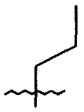
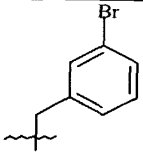
Step 2A:

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 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:

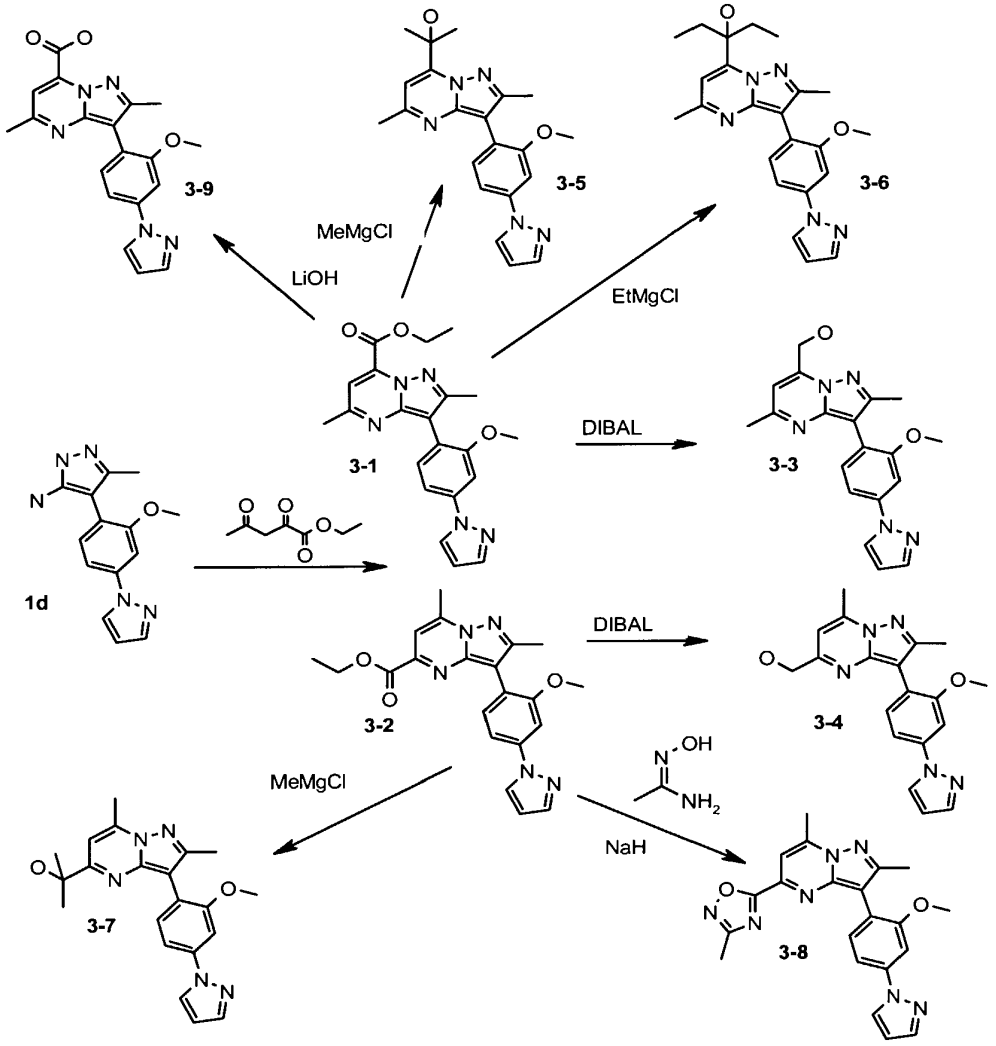


Cmpd	R_2	MW	MS	t_R	HPLC Method
2-1		361.447	361	1.286	4
2-2		375.474	375	1.499	4
2-3		333.393	333	1.542	4
2-4		375.474	375	1.278	4
2-5		389.5	390.2	8.490	2
2-6		347.42	348	6.514	2
2-7		415.417	415	7.880	2
2-8		409.491	409	6.280	2

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 uL 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:

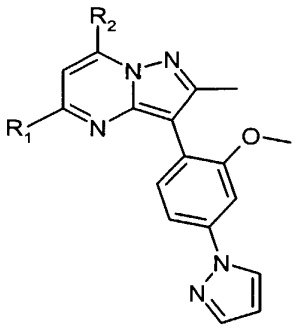
To 1.5 mL THF was added Cmpd **3-1** (30 mg) followed by CH_3MgBr (150 uL of 2 M CH_3MgBr in THF.) The reaction mixture was stirred at room temperature for 2 hr and quenched with water. The resulting material was purified by LC-MS to yield Cmpd **3-5** (3.8 mg.) Following this procedure with Cmpd **3-1** and CH_3CH_2MgBr yielded Cmpd **3-6** (4.1 mg.) after purification. Following the same reaction procedure employing Cmpd **3-2** as the starting reagent and CH_3MgBr as nucleophile afforded Cmpd **3-7** (4.0 mg) after purification.

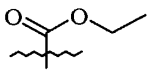
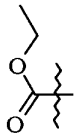
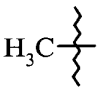
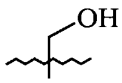
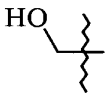
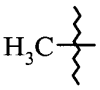
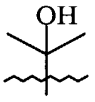
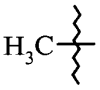
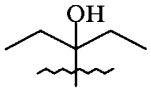
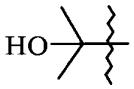
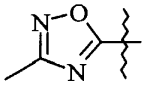
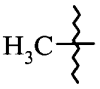
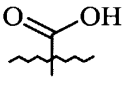
Step 3D:

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 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:

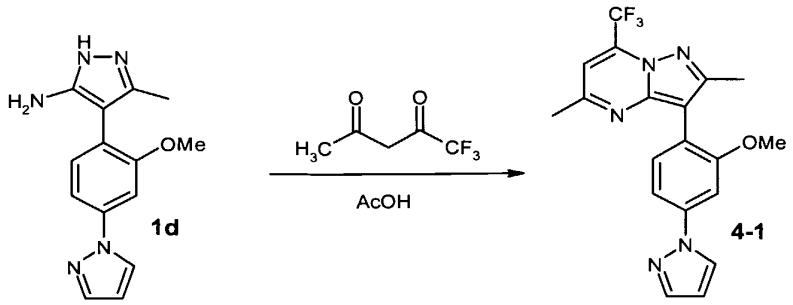
To Cmpd **3-1** (200 mg) in dioxane:water (9:1) was added LiOH (30 mg.) The reaction proceeded with stirring for 6 hr at room temperature followed by quenching to pH 4 (HCl, 4 N) and extraction between H_2O (20 mL) and EtOAc (20 mL.) The organic phase was dried over Na_2SO_4 and concentrated. The resulting 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

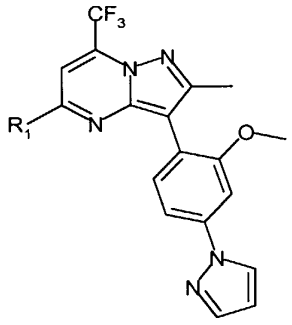
EXAMPLE 4

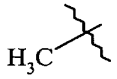
3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-TRIFLUOROMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



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:

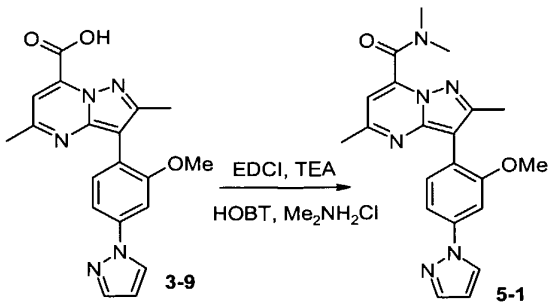


Cmpd	R_1	MW	MS	t_R*
4-1		387.363	387	6.215
4-2		415.417	415	6.928

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 5

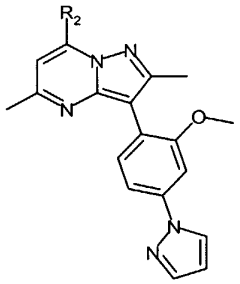
3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE-7-CARBOXYLIC ACID DIMETHYLAMIDE



3-9 5-1

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:

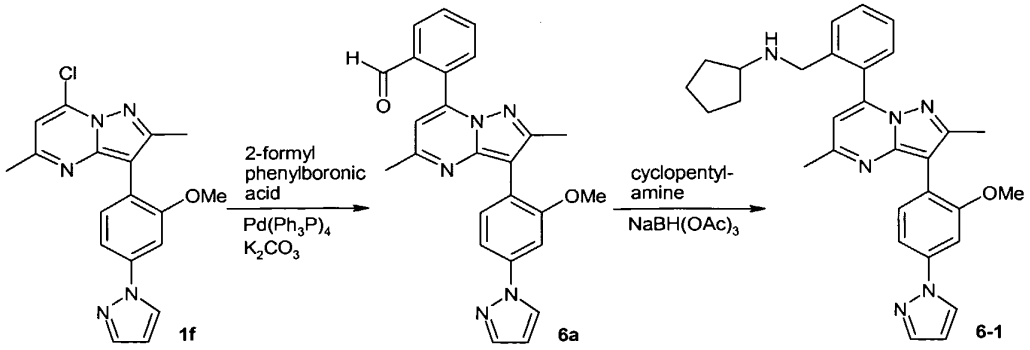


Cmpd	R_2	MW	MS	t_R*
5-1	$-C(O)N(CH_3)_2$	390.44		5.17
5-2	$-C(O)N(CH_2CH_3)_2$	418.50	419.2	6.22
5-3	$-C(O)N(CH_3)CH_2CH_3$	404.47	405.2	5.66

* 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



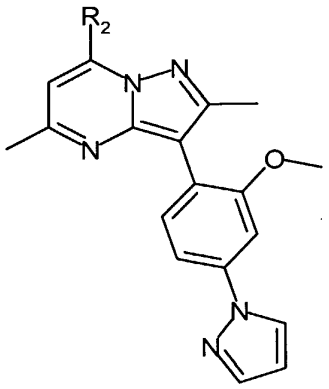
Step 6A:

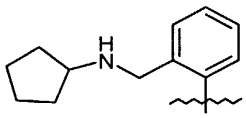
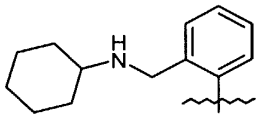
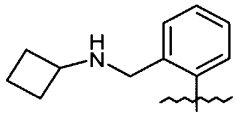
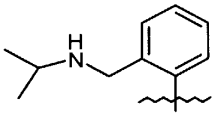
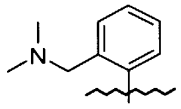
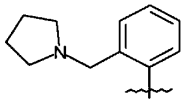
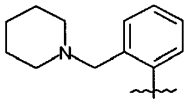
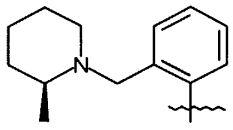
To a solution of **1f** (500 mg, 1.4 mmol, 1 eq) in 1:1 dioxane/water (6 mL) was added 2-formylphenylboronic acid (255 mg, 1.7 mmol, 1.2 eq), followed by potassium carbonate (390 mg, 2.8 mmol, 2.0 eq) and tetrakis(triphenylphosphine)palladium(0) (82 mg, 0.07 mmol, 0.05 eq). The mixture was heated in 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.

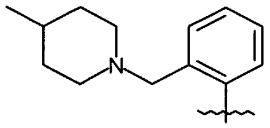
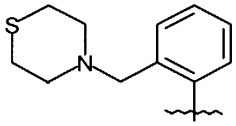
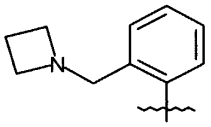
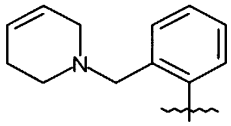
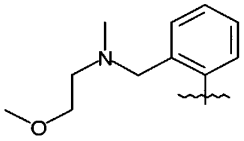
Step 6B:

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:



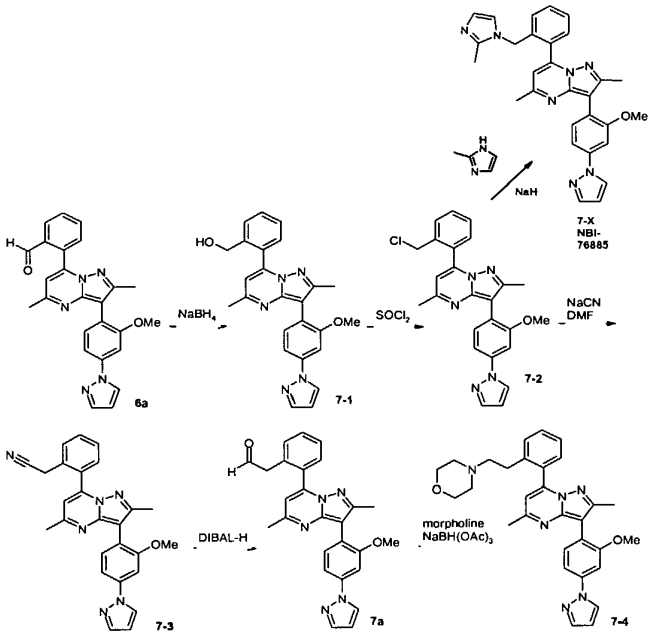
Cmpd	R_2	MW	MS	t_R*
6-1		492.62	493.4	5.69
6-2		506.65	507.4	5.95
6-3		478.60	479.1	5.49
6-4		466.59	467.1	5.33
6-5		452.559	452	4.40
6-6		478.597	478	4.70
6-7		492.624	492	4.85
6-8		506.651	506	4.74

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



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.

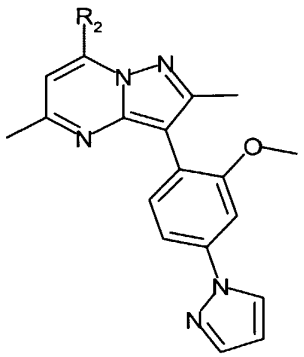
Step 7E:

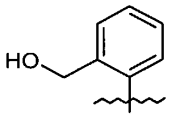
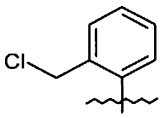
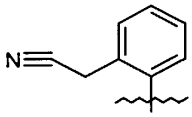
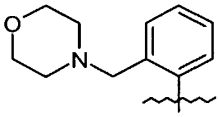
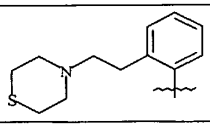
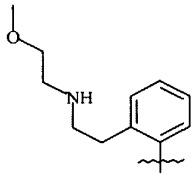
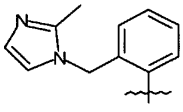
DIBAL-H (0.23 mL of a 1.5 M solution in toluene, 0.35 mmol, 3 eq) was added to a solution of **7-3** (50 mg, 0.11 mmol) in DCM (1 mL) at -78 °C. The mixture was stirred at –78 °C for 20 min, then was allowed to warm to RT. Water was added and the mixture was stirred for 10 min, then the aqueous layer 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.

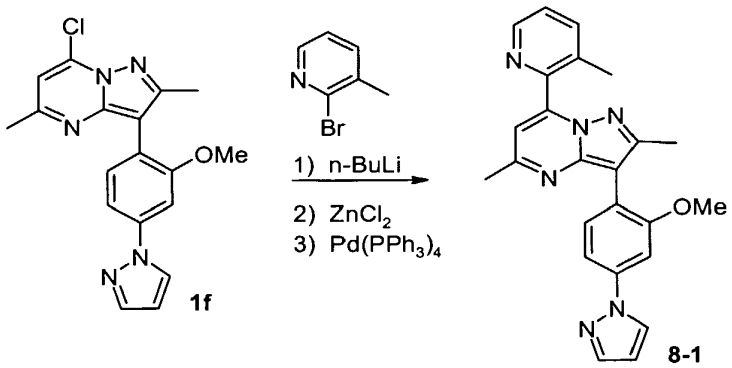
The following table summarizes the compounds of Example 7. By varying the amine employed in the reductive amination step above, Cmpds **7-5** and **7-6**, included in the table, were synthesized by the methods of Step 7E:



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

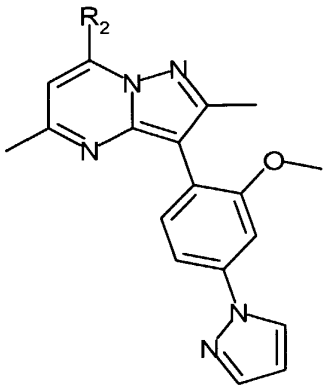
3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(3-METHYL-PYRIDIN-2-YL)-PYRAZOLO[1,5-A]PYRIMIDINE

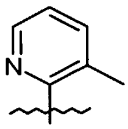
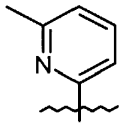
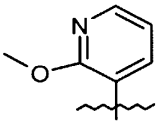
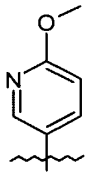
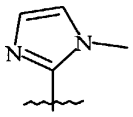
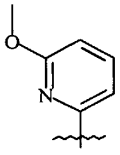
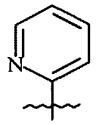


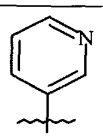
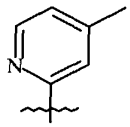
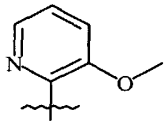
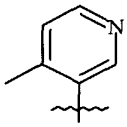
Step 8A:

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 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, 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 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:



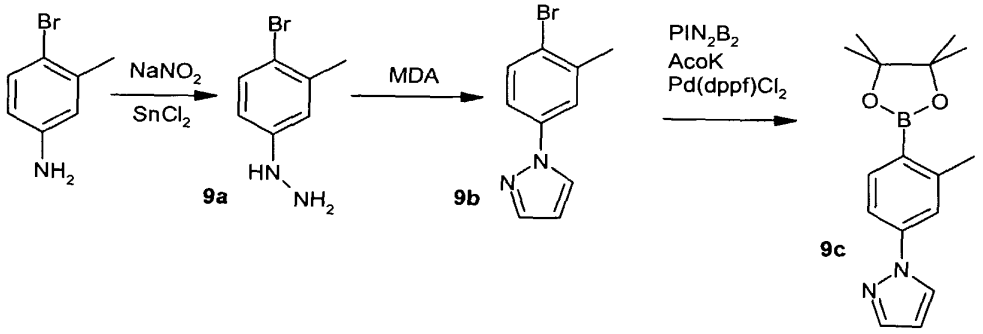
Cmpd	R_2	MW	MS	t_R*
8-1		410.48	411	5.400
8-2		410.48	411	5.770
8-3		426.48	427	5.690
8-4		440.51	441	6.240
8-5		399.456	399	4.130
8-6		426.478	426	6.410
8-7		396.452	396	5.720

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



Step 9A:

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

Step 9B:

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

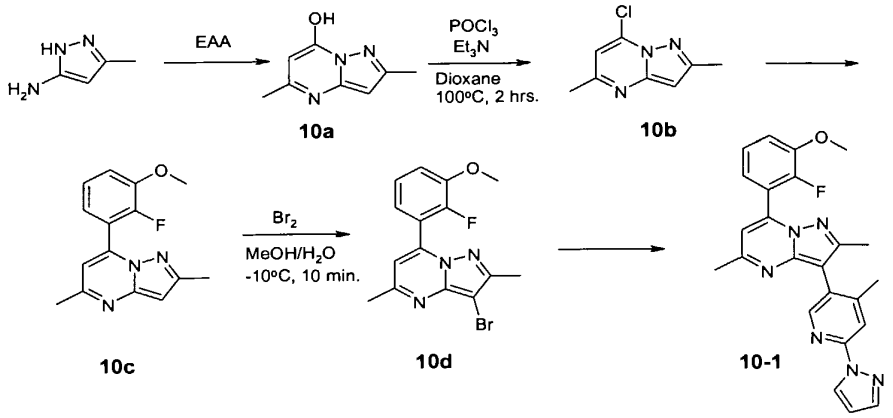
Step 9C:

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

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

EXAMPLE 10

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



Step 10A:

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

Step 10B:

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

Step 10C:

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

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

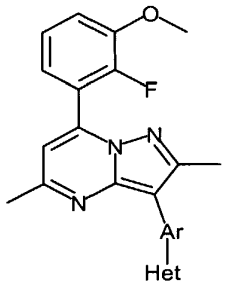
Step 10D:

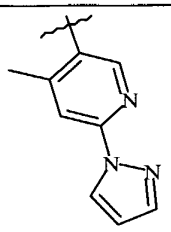
Bromine (1.77 g, 11 mmol) was added to a solution of **10c** (3.0 g, 11 mmol) in methanol (30 mL) at –10 °C. After 10 min, the mixture was filtered to collect the precipitate that had formed. The filter cake was washed with cold methanol, and was then dried under vacuum to yield **10d** (3.15 g, 83 %)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

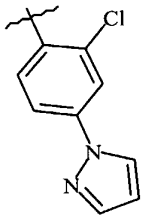
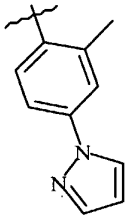
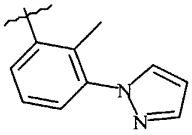
Step 10E:

Suzuki reaction of Cmpd **10d** (460 mg, 1.3 mmol) according to the procedure of Step 10C above, using Cmpd **12-1** in place of 2-fluoro-3-methoxyphenylboronic acid, yielded Cmpd **10-1** (15 mg, solid) following purification by prep HPLC/MS and silica gel chromatography (4:1 hexane/ethyl acetate eluent).

Depending on the boronate ester or acid employed in the final Suzuki reaction, the compounds listed in the following table were synthesized and purified by preparative LC-MS:



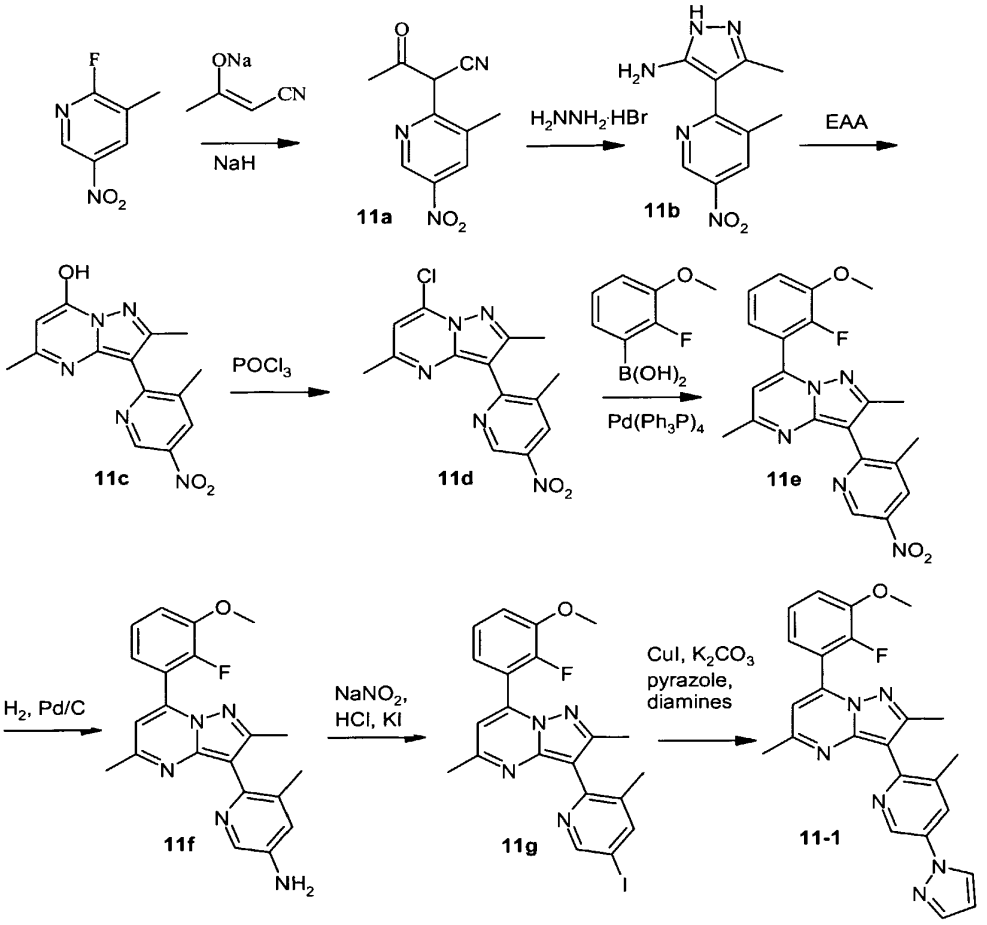
Cmpd	AR-HET	MW	MS	t_R*
10-1		428.469	429	8.110

10-2		447.899	447	6.390
10-3		427.481	427	6.330
10-4		427.481	427	7.670

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 11

7-(2-FLUORO-3-METHOXY-PHENYL)-2,5-DIMETHYL-3-(3-METHYL-5-PYRAZOL-1-YL-PYRIDIN-2-YL)-PYRAZOLO[1,5-A]PYRIMIDINE



Step 11A:

Sodium hydride (1.54 g of 60 % dispersion in oil, 38.5 mmol, 2 eq) was added to a solution of cyanoacetone sodium salt (2.5 g, 23 mmol, 1.2 eq) in DMF (40 mL) at RT. The mixture was stirred for 15 min, then a solution of 2-fluoro-3-methyl-5-nitropyridine (3.0 g, 19.2 mmol, 1.0 eq) in 10 mL DMF was added dropwise. The reaction mixture was stirred at RT for 6 hr. The reaction was quenched with 5 g ice, followed by 150 mL water and 10 mL acetic acid. The mixture was extracted with ethyl acetate, then the combined organic extracts were dried over sodium sulfate, filtered,

and concentrated. The residue was purified by silica gel chromatography using 30% ethyl acetate in hexanes as eluent, providing **11a** (1.85 g, 44 % yield) as an orange oil.

Step 11B:

A mixture of **11a** (1.8 g, 8.2 mmol, 1.0 eq), hydrazine monohydrobromide (1.0 g, 8.8 mmol, 1.1 eq), ethanol (30 mL) and water (3 mL) was heated at reflux for 17 hr. The solvent was evaporated, and the residue was purified directly by silica gel chromatography using 1:1 hexanes/ethyl acetate as eluent, obtaining **11b** (1.8 g, 94 % yield) as a yellow foam.

Step 11C:

A mixture of **11b** (1.8 g, 7.7 mmol, 1.0 eq), ethanol (15 mL), acetic acid (15 mL), and ethyl acetoacetate (1.6 g, 12.4 mmol, 1.6 eq) was heated in a sealed tube at 105 °C for 19 hr. The solvent was evaporated, and the residue was deposited on a fritted glass filter, rinsing with ether, to provide **11c** (1.0 g, 43 % yield) as a yellow solid.

Step 11D:

A mixture of **11c** (800 mg, 2.7 mmol, 1.0 eq), phosphorous oxychloride (900 mg, 5.9 mmol, 2.2 eq), and acetonitrile (15 mL) was refluxed for 3 hr. The reaction was poured onto ice, then the mixture was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with aqueous sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to provide **11d** (640 mg, 76 %) as a yellow solid.

Step 11E:

A suspension of **11d** (640 mg, 2.0 mmol,1 eq), 2-fluoro-3-methoxyphenylboronic acid (480 mg, 3.8 mmol, 1.4 eq), potassium carbonate (555 mg, 4.0 mmol, 2.0 eq), tetrakis(triphenylphosphine)palladium(0) (230 mg, 0.2 mmol, 0.1 eq) in 20 mL dioxane and 2 mL water was stirred and heated at 100 °C for 16 hr. Water (50 mL) was added and the mixture was extracted with ethyl acetate (50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was triturated with methanol to obtain **11e** (300 mg, 37 %) as a yellow solid.

Step 11F:

10 % Pd/C (100 mg) was added to a nitrogen-sparged solution of **11e** (300 mg, 0.74 mmol, 1.0 eq) in 20 mL ethanol and 10 mL THF. The mixture was shaken in a Parr shaker under 40 psi hydrogen gas at RT for 6 hr. The mixture was purged with nitrogen and filtered. The filtrate was concentrated to provide **11f** (260 mg, 94% yield) as a yellow oil.

Step 11G:

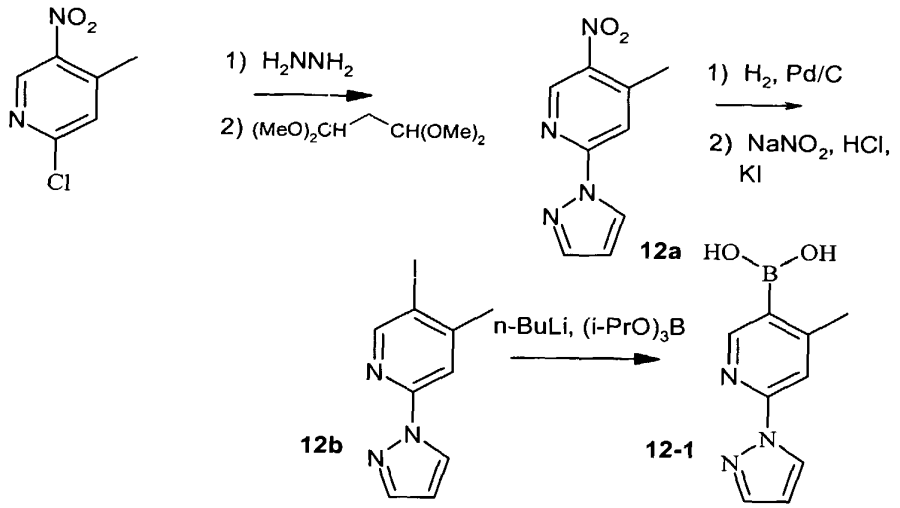
A solution of sodium nitrite (60 mg, 0.87 mmol, 1.3 eq) in water (10 mL) was added dropwise to an ice-cold solution of **11f** (260 mg, 0.69 mmol, 1.0 eq) in 4N hydrochloric acid (5 mL). The mixture was stirred at 0 °C for 1 hr, followed by addition of 10 mL of half-saturated aqueous potassium iodide. The mixture was stirred at RT for 16 hr, then 50 mL saturated aqueous sodium bicarbonate solution was added and the mixture was extracted 2x 50 mL ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, concentrated and the residue purified by silica gel chromatography using 4:1 hexanes/ethyl acetate as eluent, providing **11g** (170 mg, 51 % yield) as a yellow solid.

Step 11H:

To a solution of **11g** (170 mg, 0.35 mmol, 1.0 eq) in dioxane (6 mL) were added potassium carbonate (200 mg, 1.45 mmol, 4.1 eq), pyrazole (60 mg, 0.89 mmol, 2.5 eq), copper(I) iodide (60 mg, 0.32 mmol, 0.9 eq), trans-1,2-diaminocyclohexane (36 mg, 0.32 mmol, 0.9 eq), and N,N'-dimethylethylenediamine (28 mg, 0.32 mmol, 0.9 eq). The mixture was stirred and heated in a sealed tube at 100 °C for 19 hr. The reaction mixture was filtered through a Celite® pad, concentrated, and purified by prep HPLC/MS to obtain Cmpd **11-1** (70 mg, 37 % yield) as a TFA salt; MW: 428.47; LC/MS: 429 $[MH]^+$; t_R: 5.390, Anal. Meth. 2.

EXAMPLE 12

4-METHYL-2-PYRAZOL-1-YL-5-PYRIDYLBORONIC ACID



Step 12A:

2-Chloro-4-methyl-5-nitropyridine (5.0 g, 29 mmol, 1.0 eq) was dissolved in 50 mL hydrazine solution (1M solution in THF) and the mixture was stirred and heated in a sealed tube at 80 °C for 22 hr. The cooled reaction mixture was filtered, and the solid obtained was washed with ether to provide 5.7 g of a greenish brown solid.

A mixture of this solid (5.7 g, 24 mmol, 1.0 eq), malonaldehyde bis(dimethylacetal) (5.9 g, 31 mmol, 1.3 eq), and acetic acid (50 mL) was stirred and heated in a sealed tube at 80 °C for 5 hr. The solvent was evaporated, then aqueous sodium bicarbonate solution (200 mL) was added and the mixture was extracted with 2 x 200 mL ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was recrystallized from ethanol to obtain **12a** (2.6 g, 53 % yield) as a yellow solid.

Step 12B:

A mixture of **12a** (2.6 g, 13 mmol) and 10 % Pd/C (200 mg) in 30 mL of 1:1 THF/methanol was shaken in a Parr apparatus under 40 psi hydrogen at RT for 2 hr. The reaction mixture was filtered through a Celite® pad and the filtrate concentrated to a light green oil. The oil was resuspended in 10 mL of 3N hydrobromic acid, cooled

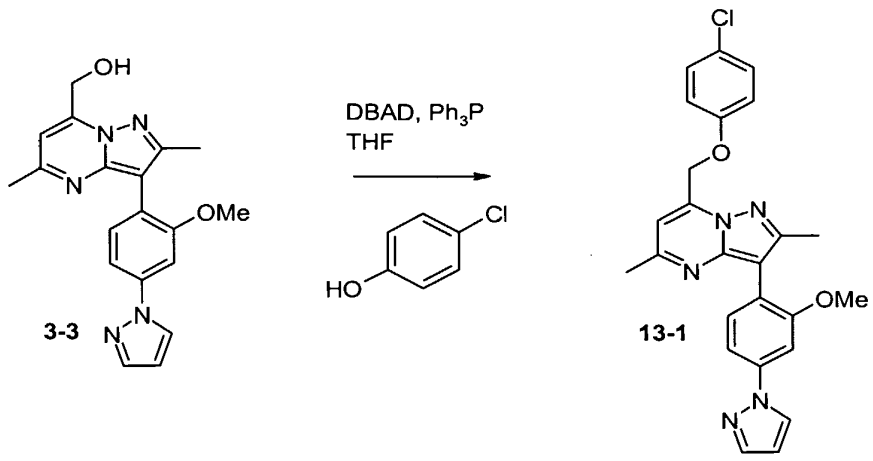
to 0 °C, then treated dropwise with a solution of sodium nitrite (835 mg, 12 mmol, 1.1 eq) in 2 mL water. The mixture was stirred at 0 °C for 1 hr, then 2 mL of half-saturated potassium iodide was added and the mixture was stirred at RT for 22 hr. Saturated aqueous sodium bicarbonate solution was added, then the mixture was extracted with 2x 100 mL ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using 4:1 hexanes/ethyl acetate as eluent, to provide **12b** (1.23 g, 33 %) as a yellow solid.

Step 12C:

n-Butyllithium (1.8 mL of a 2.0 M solution in pentane, 3.6 mmol) was added dropwise to a solution of Cmpd **12b** (600 mg, 2.1 mmol) and triisopropylborate (900 mg, 4.8 mmol) in 5 mL THF at –78 °C. The mixture was allowed to warm to RT over 1 hr, then the mixture was cooled to –78 °C and treated with additional triisopropylborate (400 mg, 2.1 mmol), followed by additional n-butyllithium (0.5 mL of a 2.0 M solution in pentane, 1.0 mmol). The mixture again was allowed to warm to RT over 1 hr, then 0.8 mL of 1N hydrochloric acid was added and the mixture was stirred for 1 hr. The mixture was filtered, rinsing the solid with methanol and ethyl acetate, then the filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 1:1 hexanes/ethyl acetate to provide Cmpd **12-1** (220 mg, 52 % yield) as a red solid.

EXAMPLE 13

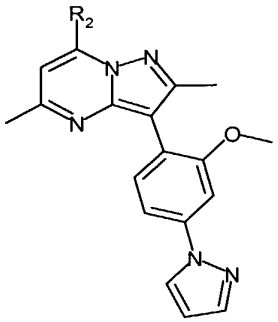
7-(4-CHLORO-PHENOXYMETHYL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

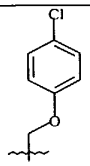
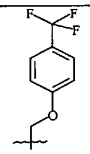
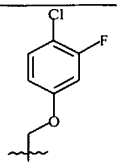
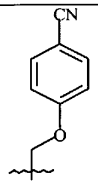
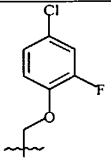
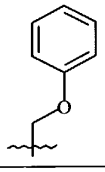


Step 13A:

To a solution of Cmpd **3-3** (25 mg, 0.072 mmol, 1 eq) in THF (1.5 mL) were added di-*tert*-butylazodicarboxylate (30 mg, 0.11 mmol, 1.5 eq), triphenylphosphine (30 mg, 0.11 mmol, 1.5 eq) and 4-chlorophenol (30 mg, 0.023 mmol, 3.3 eq). The mixture was stirred at RT for 17 hr, then the solvent was evaporated and the residue was purified by silica gel chromatography, eluting with hexanes/ethyl acetate to provide Cmpd **13-1** (8 mg) as a solid.

Depending on the phenol employed, the compounds listed in the following table were synthesized and purified by preparative LC-MS:

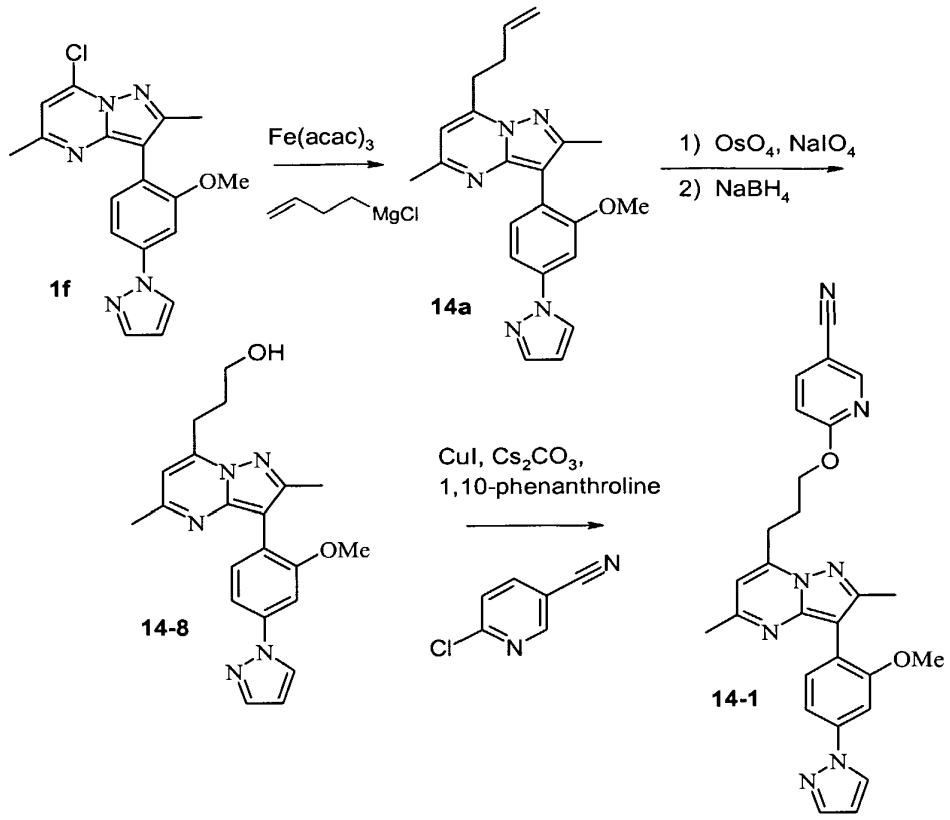


Cmpd	R_2	MW	MS	t_R*
13-1		459.935	460	9.090
13-2		493.487	494	7.690
13-3		477.925	478	9.210
13-4		450.5	451	7.850
13-5		477.925	478	9.170
13-6		425.49	426	8.420

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 14

6-{3-[3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDIN-7-YL]-PROPOXY}-NICOTINONITRILE



Step 14A:

To a solution of Cmpd **1f** (1.06 g, 3.0 mmol) and iron(III)acetylacetonate (353 mg, 1.0 mmol) in 10 mL anhydrous THF/NMP (7:1) was added slowly 3-butenylmagnesium chloride (9.0 mL of a 0.5 M solution in THF, 4.5 mmol). The reaction mixture was stirred at RT for 1 hr, then more iron(III)acetylacetonate (1.0 g, 2.8 mmol) and Grignard reagent (6.0 mL, 3.0 mmol) were added. The reaction mixture was stirred for 2 hr, then water was added. The mixture was extracted with ethyl acetate, then the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent to provide **14a** (538 mg, 48 % yield).

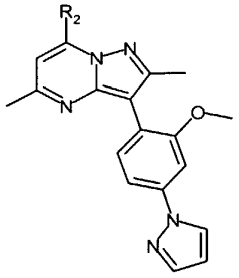
Step 14B:

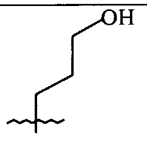
To a solution of **14a** (380 mg, 1.02 mmol) in 10 mL THF/water (4:1) was added osmium tetroxide (26 mg, 0.10 mmol) followed by sodium periodate (642 mg, 3.0 mmol) at RT. The mixture was stirred at RT for 1 hr, then ethyl acetate and water were added. The organic layer was dried over sodium sulfate, filtered, and evaporated to provide the crude aldehyde, which was dissolved in methanol (20 mL). Sodium borohydride (152 mg, 4.0 mmol) was added portionwise. After stirring at room temperature for 20 min, the reaction mixture was concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/ethyl acetate to provide Cmpd **14-1** (230 mg, 60 % yield).

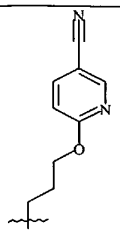
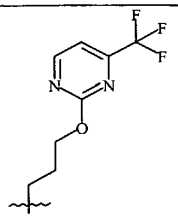
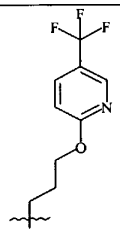
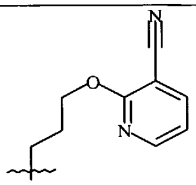
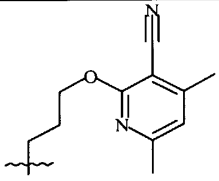
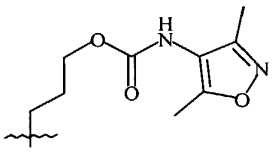
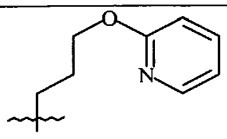
Step 14C:

A mixture of **14-1** (30 mg, 0.08 mmol, 1 eq), copper(I) iodide (15 mg, 0.08 mmol, 1 eq), cesium carbonate (52 mg, 0.16 mmol, 2 eq), and 1,10-phenanthroline (14 mg, 0.08 mmol, 1 eq) was heated in 1 mL of toluene in a sealed vial at 110 °C for 17 hr. The cooled mixture was filtered through Celite®, then concentrated. The residue was purified by silica gel chromatography using hexane/ethyl acetate as eluent to provide **14-2** (5 mg) as a solid.

Depending on the aryl halide used in the method of Step 14C, the compounds listed in the following table in additional to Cmpd **14-1** were synthesized and purified by preparative LC-MS.



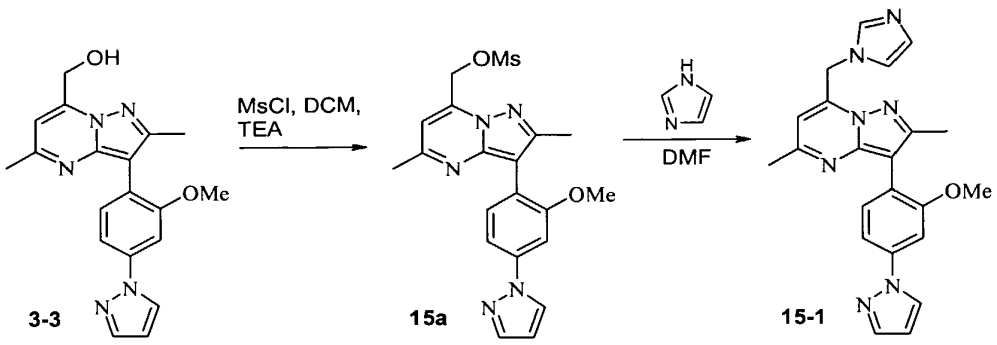
Cmpd	R_2	MW	MS	t_R*
14-1		377.446	377	5.170

Cmpd	R_2	MW	MS	t_R*
14-2		479.542	479	7.570
14-3		523.517	523	8.020
14-4		522.529	522	6.620
14-5		479.542	479	7.350
14-6		507.595	507	8.320
14-7		515.571	515	6.510
14-8		454.531	454	6.690

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 15

7-IMIDAZOL-1-YLMETHYL-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



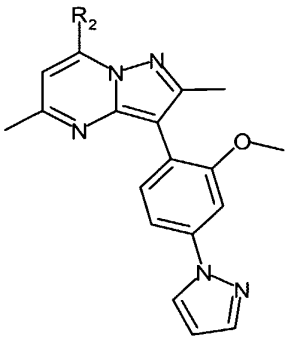
Step15A:

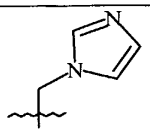
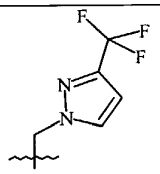
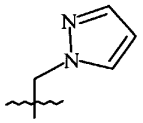
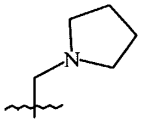
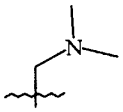
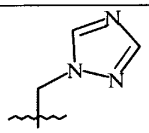
A solution of methanesulfonyl chloride (100 mg, 0.86 mmol, 1.5 eq) in DCM (0.5 mL) was added dropwise to a 0 °C solution of Cmpd **3-3** (200 mg, 0.57 mmol, 1 eq) in 5 mL DCM. The mixture was allowed to warm to RT over 1 hr, then saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with 2 x 20 mL DCM. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to obtain **15a** (180 mg, 49 % yield) as a yellow foam.

Step 15B:

Potassium carbonate (20 mg, 0.14 mmol, 2.6 eq) and imidazole (20 mg, 0.30 mmol, 5.5 eq) were added to a solution of **15a** (23 mg, 0.054 mmol, 1 eq) in DMF (1 mL). The reaction mixture was stirred at RT for 16 hr, then methanol (1 mL) was added and the reaction mixture was purified directly by preparative HPLC/MS, providing **15-1** (10 mg) as a TFA salt.

Depending on the nucleophilic heterocycle or amine employed, the compounds listed in the following table were synthesized and purified by preparative LC-MS:

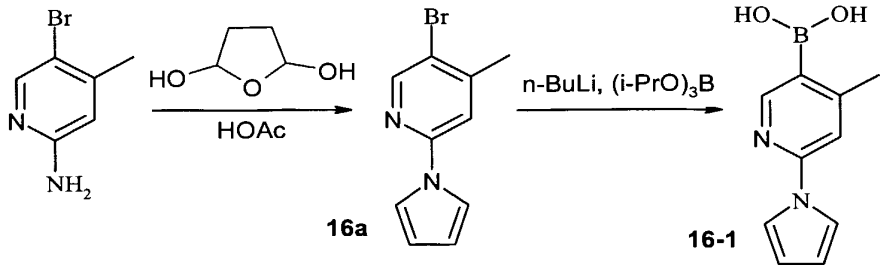


Cmpd	R_2	MW	MS	t_R*
15-1		399.456	400	4.190
15-2		467.453	468	6.320
15-3		399.456	400	5.520
15-4		402.499	403	4.110
15-5		376.462	377	3.880
15-6		400.444	401	5.330

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 16

4-METHYL-2-PYRROL-1-YL-5-PYRIDYLBORONIC ACID



Step 16A:

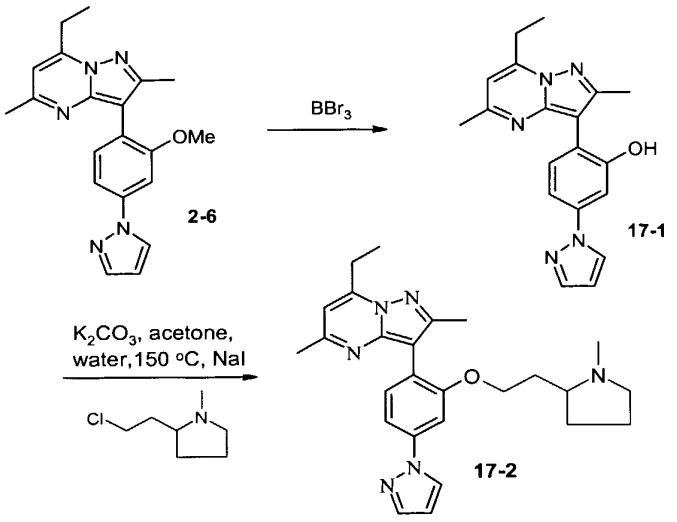
A solution of 2-amino-5-bromo-4-methylpyridine (1 g, 5.4 mmol) and 2,5-dihydroxytetrahydrofuran (2.8 g, 27 mmol) in acetic acid (10 mL) was heated at 90 °C in a sealed tube for 2 hr. The reaction mixture was concentrated and the residue was purified by silica gel chromatography using 4:1 hexanes/ethyl acetate, providing **16a** (900 mg, 71 % yield) as a light yellow oil.

Step 16B:

n-Butyllithium (3.6 mL of a 2.0 M solution in pentane, 7.2 mmol) was added dropwise to a solution of Cmpd **16a** (860 mg, 3.6 mmol) and triisopropylborate (1.4 g, 7.3 mmol) in 6 mL THF at –78 °C. The mixture was allowed to warm to RT over 1 hr, then 0.5 mL of 4N hydrochloric acid was added and the mixture was stirred for 10 min. The mixture was extracted 2x 25 mL DCM, then the organic layer was dried over sodium sulfate, filtered, and concentrated to provide **16-1** (250 mg) as a yellow oil. The aqueous layer was concentrated, then the solid residue was washed with ethanol. The combined ethanol filtrates were concentrated to provide additional **16-1** (500 mg) as a yellow oil.

EXAMPLE 17

7-ETHYL-2,5-DIMETHYL-3-{2-[2-(1-METHYL-PYRROLIDIN-2-YL)-ETHOXY]-4-PYRAZOL-1-YL-PHENYL}-PYRAZOLO[1,5-A]PYRIMIDINE



Step 17A:

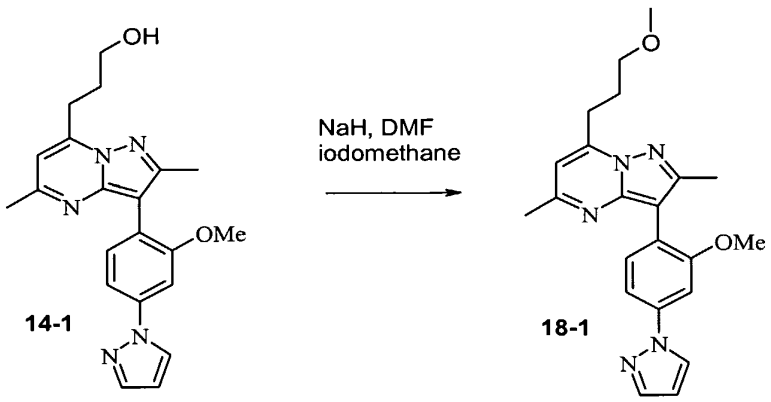
To a solution of Cmpd **2-6** (350 mg) in chloroform (5 mL) was added BBr_3 (1.0 M in DCM, 5 mL.) The mixture was stirred overnight at room temperature and quenched with water. The mixture was extracted with chloroform (2x 10 mL), then the combined organic extracts were dried over sodium sulfate, filtered, and concentrated to provide Cmpd **17-1** (280 mg) as an oil. An aliquot (10 mg) was purified by prep HPLC/MS to provide purified Cmpd **17-1** (2.9 mg.)

Step 17B:

A mixture of Cmpd **17-1** (45 mg, 0.14 mmol, 1 eq), potassium carbonate (56 mg, 0.41 mmol, 3 eq), sodium iodide (20 mg, 0.13 mmol, 1 eq), 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (39 mg, 0.21 mmol, 1.5 eq), acetone (1 mL) and water (1 mL) was heated in a sealed tube in a microwave reactor at 150 °C for 25 min. The acetone was evaporated, then the residue was diluted with methanol, filtered, and subjected directly to preparative HPLC/MS purification, yielding Cmpd **17-2** (14 mg, 20%) as a TFA salt; MW: 444.58; LC/MS: 444 $[MH]^+$; t_R: 6.010, Anal. Meth. 2.

EXAMPLE 18

7-(3-METHOXY-PROPYL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE

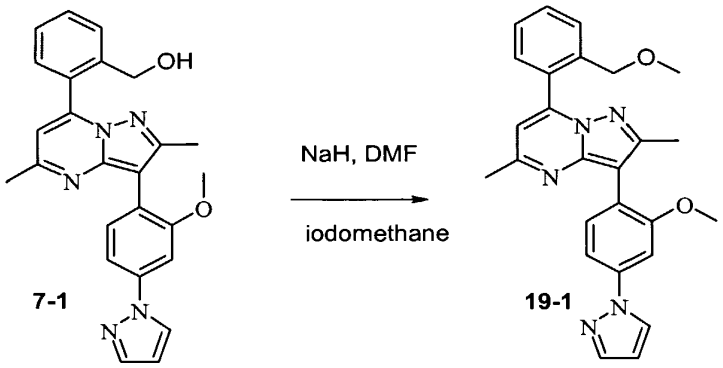


Step 18A:

To a solution of **14-1** (30 mg) in dry DMF was added NaH (10 mg, 60% dispersion). After stirring at RT for 10 min, methyliodide (0.015 mL) was added. The mixture was stirred for 1 hr, then methanol (1 mL) was added and the mixture was subjected directly to prep HPLC/MS purification, providing Cmpd **18-1** (12 mg) as a TFA salt; MW: 391.47 LC/MS: 391 $[MH]^+$; t_R: 7.050, Anal. Meth. 2.

EXAMPLE 19

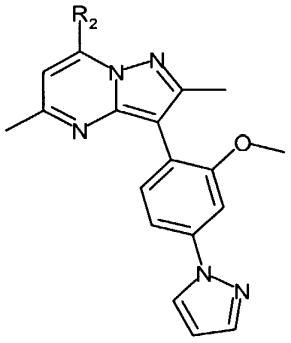
2-[7-(2-METHOXYMETHYL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDIN-3-YL]-5-PYRAZOL-1-YL-PHENOL

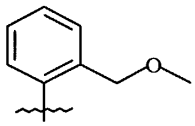


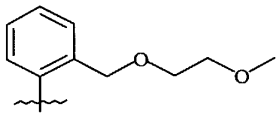
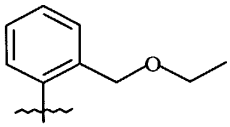
Step 19A:

The procedure of Example 18 was followed using Cmpd **7-1** as starting material

Depending on the alkyl halide employed, the compounds listed in the following table were synthesized and purified by preparative LC-MS.

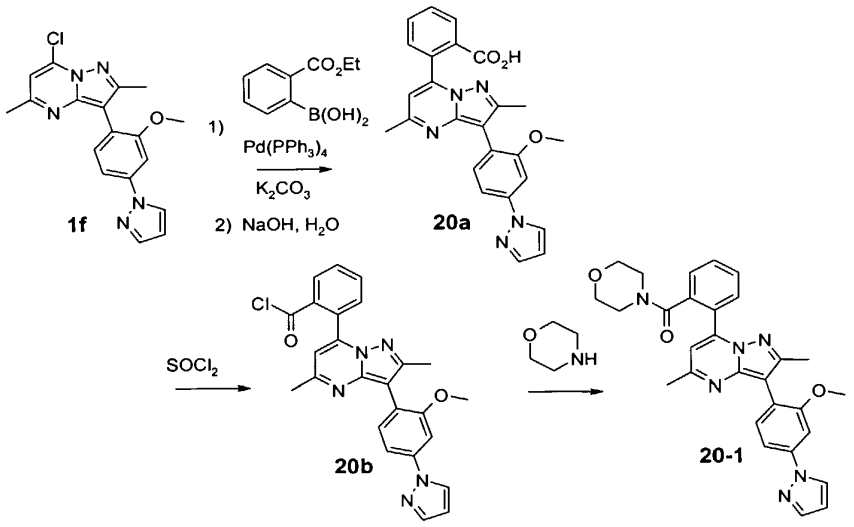


Cmpd	R_2	MW	MS	t_R*
19-1		439.517	439	6.130

Cmpd	R_2	MW	MS	t_R*
19-2		483.569	483	5.980
19-3		453.543	453	6.290

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 20



Step 20A:

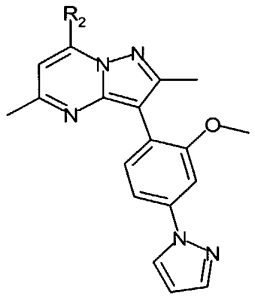
A mixture of Cmpd **1f** (710 mg, 2.0 mmol), (2-ethoxycarbonyl)phenylboronic acid (470 mg, 2.4 mmol), tetrakis (triphenylphosphine)palladium(0) (116 mg, 0.1 mmol), and potassium carbonate (550 mg, 4.0 mmol) was heated in 9:1 dioxane/water (10 mL) at 100 °C for 2.5 hr. Sodium hydroxide solution (3N, 10 mL) was added, and the mixture was stirred at 100 °C for an additional 30 min. The cooled mixture was concentrated, then water was added and the pH adjusted to 2 with hydrochloric acid. The mixture was extracted with chloroform, then the combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated to provide a crude solid, which was recrystallized from chloroform to provide Cmpd **20a** (420 mg, 48 % yield) as a yellow solid.

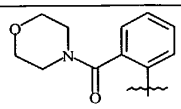
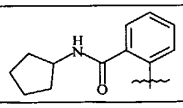
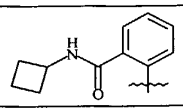
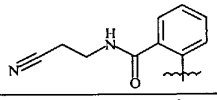
Step 20B:

Compound **20a** (420 mg, 0.96 mmol) was heated in 10 mL chloroform with thionyl chloride (1.0 mL, 14 mmol) at 70 °C for 2 hr. Volatiles were evaporated to provide Cmpd **20b** (450 mg) as a dark solid.

Step 20C:

A solution of **20b** (32 mg, 0.07 mmol) in chloroform (1 mL) was treated with morpholine (0.1 mL, 1 mmol) at RT. The mixture was allowed to sit at RT for 30 min, then the solvent was evaporated. The residue was taken up in methanol, filtered and purified directly by preparative HPLC/MS to provide **20-1** (13 mg, 30 %) as a TFA salt. Depending on the amine used, the compounds listed in the following table were synthesized and purified by preparative HPLC-MS:

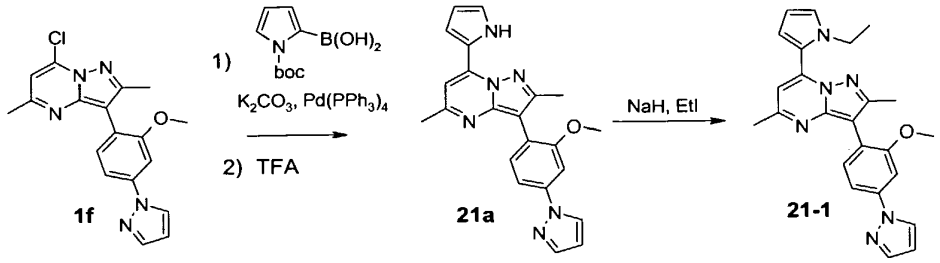


Cmpd	R_2	MW	MS	t_R*
20-1		508.579	508	6.180
20-2		506.607	506	7.050
20-3		492.58	492	6.710
20-4		491.552	491	5.840

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 21

7-(1-ETHYL-1H-PYRROL-2-YL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



Step 21A:

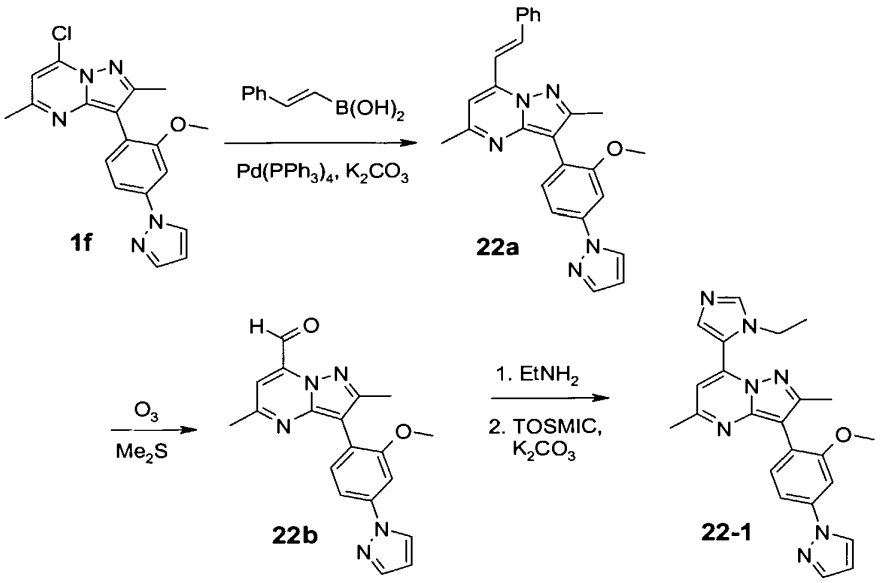
A mixture of Cmpd **1f** (210 mg, 0.6 mmol), N-Boc-pyrrole-2-boronic acid (158 mg, 0.75 mmol), tetrakis(triphenylphosphine)palladium(0) (40mg, 0.035 mmol), and potassium carbonate (166 mg, 1.2 mmol) was heated in 9:1 dioxane/water (5 mL) at 110 °C for 3 hr in a sealed tube. The cooled mixture was concentrated, then water was added and the mixture was extracted with chloroform. The combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated to provide a crude solid, which was stirred in 1:1 TFA/DCM (3 mL) for 16 hr. The mixture was diluted with ethyl acetate, then treated with aqueous ammonia. The organic layer was dried over sodium sulfate, filtered, and concentrated, then the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent to provide **21a** (110 mg, 48 % yield) as a yellow solid.

Step 21B:

To a solution of **21a** (110 mg, 0.28 mmol) in dry DMF (2 mL) was added sodium hydride (20 mg of a 60% dispersion in mineral oil, 0.5 mmol) at RT. The mixture was stirred for 5 min, then ethyl iodide (0.050 mL, 0.60 mmol) was added and the mixture was stirred at RT for 2 hr. Water and ethyl acetate were added, then the ethyl acetate layer was washed with water and brine, then dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluent to provide Cmpd **21-1** (84 mg, 73 % yield) as a yellow solid; MW: 412.50 LC/MS: 412 $[MH]^+$; t_R: 7.630, Anal. Meth. 2.

EXAMPLE 22

7-(3-ETHYL-3H-IMIDAZOL-4-YL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



Step 22A:

A mixture of Cmpd **1f** (1.50 g, 4.25 mmol), 2-phenylethenylboronic acid (692 mg, 4.68 mmol), potassium carbonate (1.17 g, 8.50 mmol), and tetrakis (triphenylphosphine)palladium(0) (250 mg, 0.22 mmol) in dioxane (9 mL) and water (1 mL) was heated at 105 °C for 16 hr. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated, and the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent to afford **22a** (1.60 g, 89 % yield) as a yellow solid.

Step 22B:

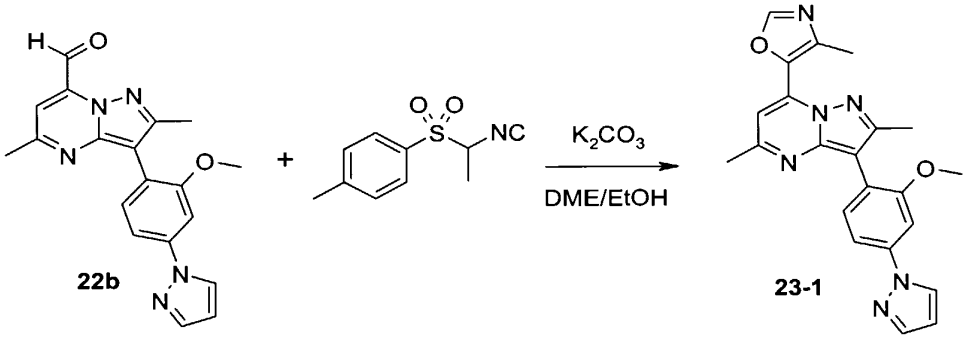
An ozone/oxygen mixture was bubbled through a solution of **22a** (1.60 g, 3.8 mmol) in dry 2:1 DCM/methanol (20 mL) at – 70 °C for 8 minutes. Dimethyl sulfide (1.5 mL) was added and the mixture was stirred and allowed to warm to RT over 16 hr. The solvent was evaporated and the residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent, providing Cmpd **22b** (1.0 g, 76 % yield) as a yellow solid.

Step 22C:

A mixture of **22b** (35 mg, 0.10 mmol), ethylamine (1.0 mL of a 2.0M solution in THF, 2.0 mmol), and magnesium sulfate in 1,2-dichloroethane was stirred at RT for 15 hr. The mixture was filtered, then the filtrate was evaporated to dryness. The residue was taken up in 1:1 ethanol/DME (2 mL), then TOSMIC (38 mg, 0.19 mmol) and potassium carbonate (55 mg, 0.4 mmol) were added and the mixture was refluxed for 17 hr. Water was added and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluent, providing Cmpd **22-1** (5 mg) as an oil; MW: 413.48 LC/MS: 413 $[MH]^+$; t_R: 5.000, Anal. Meth. 2.

EXAMPLE 23

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(4-METHYL-OXAZOL-5-YL)-PYRAZOLO[1,5-A]PYRIMIDINE

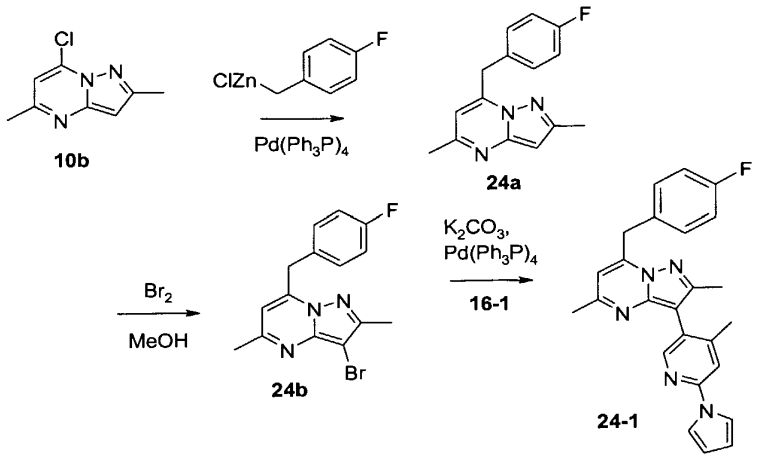


22b **23-1**

A mixture of **22b** (208 mg, 0.60 mmol), alpha-methyl-TOSMIC (251 mg, 1.2 mmol) and potassium carbonate (248 mg, 1.8 mmol) was heated in 5 mL 1:1 DME/ethanol at 80 °C for 14 hr. Water was added and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluent, providing **23-1** (60 mg, 23 %) as an oil; MW: 400.44 LC/MS: 400 $[MH]^+$; t_R: 5.250, Anal. Meth. 2.

EXAMPLE 24

7-(4-FLUORO-BENZYL)-2,5-DIMETHYL-3-(4-METHYL-6-PYRROL-1-YL-PYRIDIN-3-YL)-PYRAZOLO[1,5-A]PYRIMIDINE



Step 24A:

To a solution of 4-fluorophenylzinc chloride (20 mL of a 0.5 M solution in THF, 10 mmol) were added Cmpd **10b** (1.0 g, 5.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.26 mmol). The reaction mixture was heated at 90 °C in a sealed tube for 3 hr. The cooled reaction mixture was treated with 4N hydrochloric acid (4 mL), then water was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with 30% ethyl acetate in hexanes to obtain **24a** (1.0 g, 71 % yield) as an off-white solid.

Step 24B:

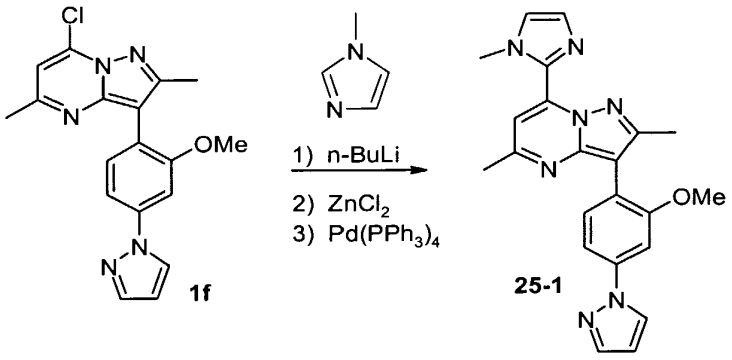
Compound **24a** (1.0 g, 3.9 mmol) was dissolved in 15 mL methanol. Bromine (0.62 g, 3.9 mmol) was added dropwise to the solution, resulting in formation of a white precipitate. The solid was collected on a fritted glass filter and rinsing with methanol. This compound was further purified by silica gel column chromatography, eluting with 4:1 hexanes/ethyl acetate to provide first a dibromination product (110 mg, 7 % yield), followed by **24b** (1.0 g, 77 % yield) as a white solid.

Step 24C:

A mixture of Cmpd **24b** (800 mg, 2.4 mmol), Cmpd **16-1** (500 mg, 2.5 mmol), tetrakis(triphenylphosphine)palladium(0) (280 mg, 0.24 mmol), and potassium carbonate (600 mg, 4.3 mmol) was heated in 9:1 dioxane/water (3.5 mL) at 95 °C for 3 hr in a sealed tube. Aqueous sodium bicarbonate solution (5 mL) was added to the cooled mixture, which was then extracted twice with DCM. The combined DCM extracts were dried over sodium sulfate, filtered, and concentrated to provide a crude oil, which was partially purified by prep HPLC/MS. The partially purified product was then chromatographed on silica gel using 4:1 hexanes/ethyl acetate as eluent, providing Cmpd **24-1** (3 mg) as a yellow solid; MW: 411.48 LC/MS: 412 $[MH]^+$; t_R: 9.160, Anal. Meth. 2.

EXAMPLE 25

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(1-METHYL-1H-IMIDAZOL-2-YL)-PYRAZOLO[1,5-A]PYRIMIDINE



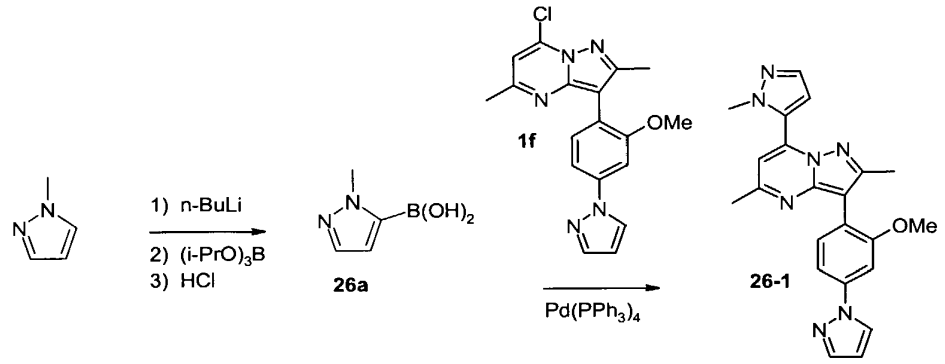
Step 25A:

To a solution of 1-methylimidazole (246 mg, 3.0 mmol) in dry THF (3 mL) cooled to –70 °C was added n-BuLi (2.5 M solution in hexane, 1.7 mL, 4.2 mmol) dropwise. The reaction mix was stirred at – 70 °C for 10 min, then $ZnCl_2$ (0.5 M solution in THF, 20 mL, 10 mmol) was added over 5 min. The mixture was stirred at -70 °C for 1 hr, then was warmed to 0 °C. Cmpd **1f** (106 mg, 0.30 mmol) and tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol) were added. The mixture was then heated to reflux for 3 hr. The cooled reaction mixture was quenched with water, the THF was evaporated and the resulting aqueous mixture was extracted with

ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and the residue was chromatographed on silica gel using ethyl acetate as eluant to give **25-1** (15 mg) as a yellow solid; HPLC retention time 4.13 min (method 2); MW 399.5; observed MS 399.

EXAMPLE 26

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-(2-METHYL-2H-PYRAZOL-3-YL)-PYRAZOLO[1,5-A]PYRIMIDINE



Step 26A:

To a solution of 1-methylpyrazole (820 mg, 10 mmol) in dry THF (20 mL) cooled to – 70 °C was added n-BuLi (1.6 M solution in hexane, 6.3 mL, 10 mmol) dropwise. The reaction mix was stirred at –70 °C for 5 min, then triisopropyl borate (2.5 mL, 11 mmol) was added over 5 min. The mixture was allowed to warm to RT over 1 hr, then 6N hydrochloric acid (5 ml) was added. The mixture was stirred for 30 min, then was evaporated to dryness to provide crude **26a** as a solid, which was used without further purification.

Step 26B:

Cmpd **1f** (530 mg, 1.5 mmol) and crude **26a** (entire amount, approximately 10 mmol) were subjected to Suzuki reaction according to the procedure of Example 1. The reaction mixture was concentrated, then water was added and the mixture was extracted with chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated, then the residue was purified by silica gel chromatography using hexanes/ethyl acetate as eluant. The product was further

purified by crystallization from acetonitrile, providing Cmpd **26-1** (280 mg) as a yellow solid; HPLC retention time 6.42 min (method 2); MW 399.5; observed MS 399)

EXAMPLE 27

CRF RECEPTOR BINDING ACTIVITY

The compounds of this invention may be evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by Grigoriadis et al. (*Mol. Pharmacol* vol50, pp679-686, 1996) and Hoare et al. (*Mol. Pharmacol* vol63 pp751-765, 2003.) By utilizing radiolabeled CRF ligands, the assay may be used to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype.

Briefly, the binding assay involves the displacement of a radiolabeled CRF ligand from the CRF receptor. More specifically, the binding assay is performed in 96-well assay plates using 1-10μg cell membranes from cells stably transfected with human CRF receptors. Each well receives about 0.05 mL assay buffer (*e.g.*, Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 2mM EGTA) containing compound of interest or a reference ligand (for example, sauvagine, urocortin I or CRF), 0.05 mL of [^{125}I] tyrosine - sauvagine (final concentration ~150 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 mL of a cell membrane suspension containing the CRF receptor. The mixture is incubated for 2 hr at 22 °C followed by separation of the bound and free radioligand by rapid filtration over glass fiber filters. Following three washes, the filters are dried and radioactivity (Auger electrons from ^{125}I) is counted using a scintillation counter. All radioligand binding data may be analyzed using the non-linear least-squares curve-fitting programs Prism (GraphPad Software Inc) or XL*fit* (ID Business Solutions Ltd).

EXAMPLE 28

CRF-STIMULATED ADENYLATE CYCLASE ACTIVITY

The compounds of the present invention may also be evaluated by various functional testing. For example, the compounds of the present invention may be screened for CRF-stimulated adenylate cyclase activity. An assay for the determination of CRF-stimulated adenylate cyclase activity may be performed as

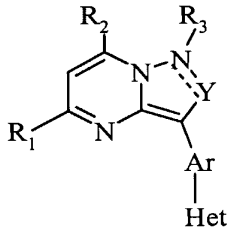
generally described by Battaglia et al. (*Synapse 1*:572, 1987) with modifications to adapt the assay to whole cell preparations.

More specifically, the standard assay mixture may contain the following in a final volume of 0.1 mL: 2 mM L-glutamine, 20 mM HEPES, and 1 mM IMBX in DMEM buffer. In stimulation studies, whole cells with the transfected CRF receptors are plated in 96-well plates and incubated for 30 min at 37 °C with various concentrations of CRF-related and unrelated peptides in order to establish the pharmacological rank-order profile of the particular receptor subtype. Following the incubation, cAMP in the samples is measured using standard commercially available kits, such as cAMP-Screen™ from Applied Biosystems. For the functional assessment of the compounds, cells and a single concentration of CRF or related peptides causing 50% stimulation of cAMP production are incubated along with various concentrations of competing compounds for 30 min at 37°C, and cAMP determined as described above.

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

WHAT IS CLAIMED IS:

1. A compound having the following structure:



or a pharmaceutically acceptable salt, ester, solvate, stereoisomer or prodrug thereof,

wherein:

"---" represents the second bond of an optional double bond;

R_1 is hydrogen, alkyl, substituted alkyl, heteroaryl, substituted heteroaryl, $-NH_2$, or halogen;

R_2 is alkyl, substituted alkyl, $-C(O)NR_7R_8$, aryl, substituted aryl, aryloxyalkyl, substituted aryloxyalkyl, heteroarylalkoxyalkyl, substituted heteroarylalkoxyalkyl, heterocyclealkyl, substituted heterocyclealkyl, arylalkyl, substituted arylalkyl, heteroaryl, or substituted heteroaryl, wherein said heteroaryl or substituted heteroaryl is connected to the pyrimidine ring via a carbon-carbon bond;

R_3 is null, hydrogen, or alkyl;

Y is $=(CR_4)-$ or $-(C=O)-$;

R_4 is hydrogen, alkyl, substituted alkyl, thioalkyl, alkylsulfinyl, or alkylsulfonyl;

Ar is phenyl, phenyl substituted with 1 or 2 R_5, pyridyl or pyridyl substituted with 1 or 2 R_5;

R_5 at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, alkylsulfonyl, or alkylsulfinyl;

Het is heteroaryl optionally substituted with 1 or 2 R_6;

R_6 at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen; and

R_7 and R_8 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, arylalkyl, substituted arylalkyl, heterocyclealkyl or substituted heterocyclealkyl; or

R_7 and R_8 taken together with the nitrogen to which they are attached form a heterocyclic ring or a substituted heterocyclic ring.

2. A compound according to claim 1 wherein R_1 is hydrogen, alkyl, substituted alkyl, $-NH_2$, or halogen.

3. A compound according to claim 1 wherein R_2 is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, wherein said heteroaryl or substituted heteroaryl is connected to the pyrimidine ring via a carbon-carbon bond.

4. A compound according to claim 1 wherein R_3 is null.

5. A compound according to claim 4 wherein Y is $=(CR_4)-$.

6. A compound according to claim 5 wherein R_4 is hydrogen, alkyl, or substituted alkyl.

7. A compound according to claim 1 wherein R_3 is hydrogen or alkyl.

8 A compound according to claim 7 wherein Y is $-(C=O)-$.

9. A compound according to claim 1 wherein Ar is phenyl substituted with 1 R_5.

10. A compound according to claim 9 wherein R_5 is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, alkylsulfonyl, or alkylsulfinyl.

11. A compound according to claim 1 wherein Het is substituted with 1 R_6.

12. A compound according to claim 11 wherein R_6 is alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen.

13. A compound according to claim 1,

wherein:

R_1 is hydrogen, alkyl or substituted alkyl;

R_3 is null;

Y is $=(CR_4)-$;

R_4 is hydrogen, alkyl or substituted alkyl;

Ar is phenyl substituted with one R_5;

R_5 is alkyl, aubstituted alkyl, alkoxy or substituted alkoxy; and

Het is heteroaryl.

14. A compound according to claim 13,

wherein:

R_1 is lower alkyl;

R_4 is lower alkyl;

R_5 is alkoxy; and

Het is pyrazolyl.

15. A compound according to claim 14,

wherein:

R_1 is methyl;

R_4 is methyl; and

R_5 is methoxy.

16. A compound according to claim15,

wherein:

R_2 is alkyl, substituted arylalkyl, substituted aryl, heteroaryl, substituted heteroaryl, substituted heteroaryloxyalkyl, heteroarylalkyl or substituted heteroarylalkyl.

17. A compound according to claim 16,

wherein:

R_2 is substituted arylalkyl, substituted aryl, heteroaryl or substituted heteroaryl.

18. A compound according to claim 17,

wherein:

R_2 is substituted benzyl, substituted phenyl, substituted pyrazolyl, pyridinyl or substituted pyridinyl.

19. A compound according to claim 18,

wherein:

R_2 is substituted pyrazolyl, pyridinyl or substituted pyridinyl.

20. A compound according to claim 19,

wherein:

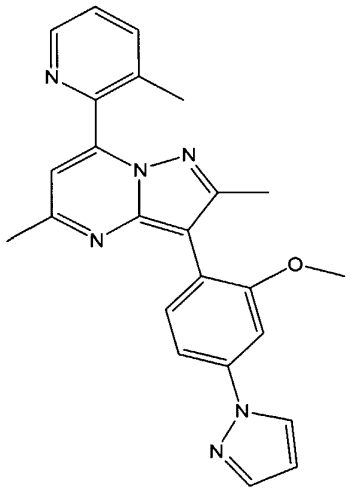
R_2 is substituted pyridinyl.

21. A compound according to claim 20,

wherein:

R_2 is methyl substituted pyridinyl or methoxy substituted pyridinyl.

22. A compound according to claim 21, wherein said compound is represented by the formula:



23. A pharmaceutical composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent.

24. A method for treating a disorder manifesting hypersecretion of CRF in a mammal comprising administering to the animal an effective amount of a pharmaceutical composition according to claim 23.

25. A method according to claim 24, wherein the disorder is stroke.

26. A method according to claim 24, wherein the disorder is depression.

27. A method according to claim 24, wherein the disorder is an anxiety-related disorder.

28. A method according to claim 24, wherein the disorder is obsessive-compulsive disorder.

29. A method according to claim 24, wherein the disorder is irritable bowel syndrome.

30. A method according to claim 24, wherein the disorder is anorexia nervosa.

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/IB2004/004234

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	US 6 313 124 B1 (HE LIQI ET AL) 6 November 2001 (2001-11-06) cited in the application column 10, lines24ff	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, line26	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

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2005	27/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Wolf, C

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/004234

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: claims 24-30 in respect of industrial applicability
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 24-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/IB2004/004234

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Information on patent family members

Intern. ial Application No
PCT/IB2004/004234

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(30) Priority Data:
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(71) Applicant *(for all designated States except US)*: **PHARMACIA CORPORATION** [US/US]; Global Patent Department, 700 Chesterfield Parkway West, Chesterfield, MO 63017-1732 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **ARNERIC, Stephen, P.** [US/US]; 10501 Timber Ridge Drive, Milan, MI 48160 (US).

(74) Agents: **PETRILLO, Kathleen, M.** et al.; Senniger Powers, #1 Metropolitan Square, 16th Floor, St. Louis, MO 63102 (US).

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Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

(57) **Abstract:** The present invention provides compositions and methods for the treatment of ischemic mediated central nervous system disorder or injury. More particularly, the invention provides a combination therapy for the treatment of a central nervous system ischemic mediated disorder or injury comprising the administration to a subject of a cyclooxygenase-2 selective inhibitor and a corticotropin releasing factor antagonist or a pharmaceutically acceptable salt or a prodrug thereof.

WO 2005/020910 A2

COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

FIELD OF THE INVENTION

[0001] The present invention provides compositions and methods for the treatment of reduced blood flow to the central nervous system. More particularly, the invention is directed toward a combination therapy for the treatment or prevention of ischemic-mediated central nervous system disorders or injury, including ischemic stroke, comprising the administration to a subject of a cyclooxygenase-2 selective inhibitor in combination with a corticotropin releasing factor antagonist.

BACKGROUND OF THE INVENTION

[0002] The continued increase in the incidence of ischemic-mediated central nervous system damage, including ischemic stroke, provides compelling evidence that there is a continuing need for better treatment strategies. Stroke, for example, is consistently the second or the third leading cause of death annually and the leading producer of disability among adults in the United States and western countries. Moreover, roughly 10% of patients with stroke become heavily handicapped, often needing attendant care.

[0003] The pathology underlying ischemic-mediated central nervous system injury has been elucidated. Generally speaking, the normal amount of perfusion to brain gray matter is 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs only when the flow of blood falls below a certain level (approximately 8-10 mL/100 g of brain tissue/min), while at slightly higher levels the tissue remains alive but not able to function. For example, most strokes culminate in a core area of cell death (infarction) in which blood flow is so drastically reduced that the cells usually cannot recover. This threshold seems to occur when cerebral blood flow is 20 percent of normal or less. Without neuroprotective agents, nerve cells facing 80 to 100 percent ischemia will be irreversibly damaged within a few minutes. Surrounding the ischemic core is another area of tissue called the "ischemic penumbra" or "transitional zone" in which cerebral blood flow is between 20 and 50 percent of normal. Cells in this area are endangered, but not yet irreversibly damaged. Thus in the acute stroke, the affected central core brain tissue may die while the more peripheral tissues

remain alive for many years after the initial insult, depending on the amount of blood the brain tissue receives.

[0004] At the cellular level, if left untreated, brain or spinal cell injury and death progress in a stepwise manner rapidly within the core infarction, and over time within the ischemic penumbra. Without adequate blood supply, brain or spinal cells lose their ability to produce energy, particularly adenosine triphosphate (ATP). When this energy failure occurs, brain or spinal cells become damaged and will die if critical thresholds are reached. Immediate cell death within the ischemic core is typically necrotic, while cell death in the penumbra may be either necrotic or apoptotic. It is believed that there are an immense number of mechanisms at work causing brain or spinal cell damage and death following energy failure. Each of these mechanisms represents a potential route for intervention. One of the ways brain cells respond to energy failure is by elevating the concentration of intracellular calcium. Worsening this and driving the concentrations to dangerous levels is the process of excitotoxicity, in which brain cells release excessive amounts of glutamate, a neurotransmitter. This stimulates chemical and electrical activities in receptors on other brain cells, which leads to the degradation and destruction of vital cellular structures. Brain cells ultimately die as a result of the actions of calcium-activated proteases (enzymes which digest cell proteins), lipases (enzymes which digest cell membranes) and free radicals formed as a result of the ischemic cascade.

[0005] No drug therapy has yet been proven completely effective in preventing brain damage from cerebral ischemia. Interventions have been directed toward salvaging the ischemic penumbra and reducing its size. Restoration of blood flow is the first step toward rescuing the tissue within the penumbra. Therefore, timely recanalization of an occluded vessel to restore perfusion in both the penumbra and in the ischemic core is one treatment option employed. Partial recanalization also markedly reduces the size of the penumbra as well. Moreover, intravenous tissue plasminogen activator and other thrombolytic agents have been shown to have clinical benefit if they are administered within a few hours of symptom onset. Beyond this narrow time window, however, the likelihood of beneficial effects is reduced and hemorrhagic complications related to thrombolytic agents become excessive, seriously compromising their therapeutic value. Hypothermia decreases the size of the ischemic insult in both anecdotal clinical and laboratory reports. In addition, a wide variety of agents have been shown to reduce infarct volume in animal models. These agents

include pharmacologic interventions that involve thrombolysis, calcium channel blockade, and cell membrane receptor antagonism have been studied and have been found to be beneficial in animal cortical stroke models. But there is a continuing need for improved treatment regimens following ischemic-mediated central nervous system injury.

[0006] Corticotropin releasing factor ("CRF"), also referred to as corticotropin releasing hormone ("CRH"), is a 41 amino acid neuropeptide hormone. This peptide is the major physiologic regulator of the basal and stress-induced production and release of adrenocorticotropic hormone ("ATCH"), β-endorphin, and other peptides from the pituitary via binding of CRF to its several receptors. ACTH release leads to the release of cortisol and other adrenal steroids. Important functions affected by the action of CRF include behavior, temperature regulation, food intake, reproduction, memory and learning, and can also induce seizures (Wong et al., *NeuroReport*, 6:13 (1995) 1785-1788 Increasing evidence exists to implicate the involvement of CRF in the pathogenesis of ischemic brain damage (Mackay et al., J. Cerebral Blood Flow and Metabolism (2001) 21:1208-1214; and DeVries et al. *Proc. Nat'l. Academy Science*, (2001) 98:11824-11828). CRF has also been implicated as being neurotoxic, being involved in neurodegeneration following cerebral ischemia (Lyons et al., *Brain Research*, 545 (1991) 339-342); Wong et al. (1995)). Additionally, several authors have noted that in humans, post-stroke concentrations of cortisol are predictive of stoke outcome, high cortisol concentrations being associated with increased morbidity and mortality (Feibel et al., *JAMA* (1977) 238: 1374-1376; Olsson, t., *J. Int. Med.* (1990) 228: 177-181).

[0007] Several recent studies have found that the administration of a corticotropin releasing factor antagonist reduces the extent of stroke-induced brain damage when administered to a subject shortly before or after the onset of the ischemic cascade. In one study, it was shown that a low dose of the corticotropin releasing factor antagonist α-helical CRF 9-41 in combination with a vehicle administered via injection either 30 minutes before or 10 minutes after a unilateral, permanent middle cerebral artery occlusion (MCAo) could markedly inhibit (by over 60%) the volume of the infarction (Strijbos, et al., *Brain Research*, 656 (1994) pp. 405-408). Corticotropin releasing factor antagonists, and in particular α-helical CRF, have also been found to demonstrate a neuroprotective effect in a dose-dependent manner (Lyons et al. (1991)). In addition, it appears that corticotropin releasing factor antagonists demonstrate an

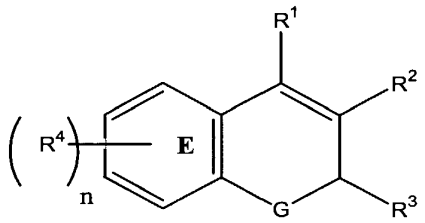
ability to inhibit neuronal damage induced by pharmacological activation of NMDA receptors , particularly in the striatum, indicating that NMDA receptor-mediated neurotoxicity is at least in part due to the release of endogenous corticotropin releasing factor (Strijbos et al. (1994)).

[0008] Moreover, several studies indicate that cyclooxygenase-2 is involved in the inflammatory component of the ischemic cascade. Cyclooxygenase-2 expression is known to be induced in the central nervous system following ischemic injury. In one study, it was shown that treatment with a cyclooxygenase-2 selective inhibitor reduced infarct volume in mice subjected to ischemic brain injury (Nagayama et al., (1999) J. Cereb. Blood Flow Metab.19(11):1213-19). A similar study showed that cyclooxygenase-2 deficient mice have a significant reduction in brain injury produced by occlusion of the middle cerebral artery when compared to mice that express cyclooxygenase-2 (Iadecola et al., (2001) PNAS 98:1294-1299). Another study demonstrated that treatment with cyclooxygenase-2 selective inhibitor results in improved behavioral deficits induced by reversible spinal ischemia in rabbits (Lapchak et al., (2001) Stroke 32(5):1220-1230).

SUMMARY OF THE INVENTION

[0009] Among the several aspects of the invention is provided a method for the treatment of ischemic mediated central nervous system disorders in a subject. The method comprises administering to the subject a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof in combination with a corticotropin releasing factor antagonist or a pharmaceutically acceptable salt or a prodrug thereof.

[0010] In one embodiment, the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof is a member of the chromene class of compounds. For example, the chromene compound may be a compound of the formula



(I)

[0011] wherein:

[0012] n is an integer which is 0, 1, 2, 3 or 4;

[0013] G is O, S or NR^a;

[0014] R^a is alkyl;

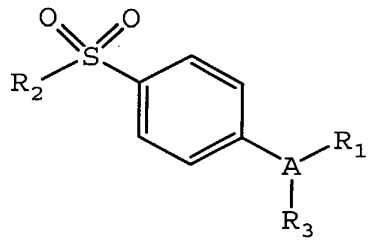
[0015] R^1 is H or aryl;

[0016] R^2 is carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl or alkoxycarbonyl;

[0017] R^3 is haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro or alkylsulfonyl; and

[0018] each R^4 is independently H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, or alkylcarbonyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0019] In another embodiment, the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof comprises a compound of the formula



[0020] wherein:

[0021] A is a partially unsaturated or unsaturated heterocyclyl ring or a partially unsaturated or unsaturated carbocyclic ring;

[0022] R_1 is heterocyclyl, cycloalkyl, cycloalkenyl or aryl, wherein R_1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[0023] R^2 is methyl or amino; and

[0024] R^3 is H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, or N-alkyl-N-arylaminosulfonyl.

[0025] In yet another embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41, antalarmin, CP-154,526, astressin, NBI 27914, and R121919.

[0026] Other aspects of the invention are described in more detail below.

ABBREVIATIONS AND DEFINITIONS

[0027] The term "acyl" is a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, and trifluoroacetyl.

[0028] The term "alkenyl" is a linear or branched radical having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl" also are radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

[0029] The terms "alkoxy" and "alkyloxy" are linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

[0030] The term "alkoxyalkyl" is an alkyl radical having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

[0031] The term "alkoxycarbonyl" is a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl porions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

[0032] Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" is a linear, cyclic or branched radical having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

[0033] The term "alkylamino" is an amino group that has been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

[0034] The term "alkylaminoalkyl" is a radical having one or more alkyl radicals attached to an aminoalkyl radical.

[0035] The term "alkylaminocarbonyl" is an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above.

[0036] The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl

radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl.

[0037] The term "alkylthio" is a radical containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio.

[0038] The term "alkylthioalkyl" is a radical containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

[0039] The term "alkylsulfinyl" is a radical containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

[0040] The term "alkynyl" is a linear or branched radical having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

[0041] The term "aminoalkyl" is an alkyl radical substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like.

[0042] The term "aminocarbonyl" is an amide group of the formula -C(=O)NH2.

[0043] The term "aralkoxy" is an aralkyl radical attached through an oxygen atom to other radicals.

[0044] The term "aralkoxyalkyl" is an aralkoxy radical attached through an oxygen atom to an alkyl radical.

[0045] The term "aralkyl" is an aryl-substituted alkyl radical such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl

may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

[0046] The term "aralkylamino" is an aralkyl radical attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" are amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

[0047] The term "aralkylthio" is an aralkyl radical attached to a sulfur atom.

[0048] The term "aralkylthioalkyl" is an aralkylthio radical attached through a sulfur atom to an alkyl radical.

[0049] The term "aroyl" is an aryl radical with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted.

[0050] The term "aryl", alone or in combination, is a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

[0051] The term "arylamino" is an amino group, which has been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

[0052] The term "aryloxyalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent oxygen atom.

[0053] The term "arylthioalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

[0054] The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", is -(C=O)-.

[0055] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", is -CO2H.

[0056] The term "carboxyalkyl" is an alkyl radical substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which are lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl.

[0057] The term "corticotropin releasing factor" and "corticotropin releasing hormone" both refer to the same 41 amino acid polypeptide as described herein and are used interchangeably without consequence.

[0058] The term "corticotropin releasing factor antagonist" or alternatively "corticotropin releasing hormone antagonist" is any peptide or non-peptide substance that tends to nullify the action of corticotropin releasing factor or that binds to a cell receptor to which corticotropin releasing factor would otherwise be able to bind and does not elicit a biological response. Corticotropin releasing factor antagonists can include, for example, peptide and non-peptide antagonists, including the monocyclic five membered and six membered ring antagonists, and antagonists from the fused bicyclic, fused tricyclic, polycyclic, and acyclic systems. Specific examples of such corticotropin releasing factor antagonists include, for example, α-helical CRF 9-41, antalarmin, CP-154,526, astressin, NBI 27914, and R121919. Furthermore, a corticotropin releasing factor antagonist may bind any of the corticotropin releasing factor receptors, including, for example, CRF_1, CRF_2, and CRF-BP receptors.

[0059] The term "cycloalkenyl" is a partially unsaturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl.

[0060] The term "cycloalkyl" is a saturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0061] The term "cyclooxygenase-2 selective inhibitor" is a compound able to selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Typically, it includes compounds that have a cyclooxygenase-2 IC_{50} of less than about 0.2 micro molar, and also have a selectivity ratio of cyclooxygenase-1 (COX-1) IC_{50} to cyclooxygenase-2 (COX-2) IC_{50} of at least about 5, more typically of at least about 50, and even more typically, of at least about 100. Moreover, the cyclooxygenase-2 selective inhibitors as

described herein have a cyclooxygenase-1 IC_{50} of greater than about 1 micro molar, and more preferably of greater than 10 micro molar. Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid used in the present method may inhibit enzyme activity through a variety of mechanisms. By the way of example, and without limitation, the inhibitors used in the methods described herein may block the enzyme activity directly by acting as a substrate for the enzyme.

[0062] The term "halo" is a halogen such as fluorine, chlorine, bromine or iodine.

[0063] The term "haloalkyl" is a radical wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically included are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" is a radical having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

[0064] The term "heteroaryl" is an unsaturated heterocyclyl radical. Examples of unsaturated heterocyclyl radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-

membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also includes radicals where heterocyclyl radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino.

[0065] The term "heterocyclyl" is a saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radical, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

[0066] The term "heterocyclylalkyl" is a saturated and partially unsaturated heterocyclyl-substituted alkyl radical, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

[0067] The term "hydrido" is a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH2-) radical.

[0068] The term "hydroxyalkyl" is a linear or branched alkyl radical having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

[0069] The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product; that is

the "pharmaceutically acceptable" material is relatively safe and/or non-toxic, though not necessarily providing a separable therapeutic benefit by itself. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiologically acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzy1ethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[0070] The term "prodrug" refers to a chemical compound that can be converted into a therapeutic compound by metabolic or simple chemical processes within the body of the subject. For example, a class of prodrugs of COX-2 inhibitors is described in US Patent No. 5,932,598, herein incorporated by reference.

[0071] The term "subject" for purposes of treatment includes any human or animal subject who is need of treatment for an ischemic mediated central nervous system disorder or injury or who is at risk for developing an ischemic mediated central nervous system disorder or injury. The subject can be a domestic livestock species, a laboratory animal species, a zoo animal or a companion animal. In one embodiment, the subject is a mammal. In another embodiment, the mammal is a human being.

[0072] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, is a divalent radical $-SO_2-$. "Alkylsulfonyl" is an alkyl radical attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" are NH_2O_2S-.

[0073] The phrase "therapeutically-effective" is intended to qualify the amount of each agent (i.e. the amount of cyclooxygenase-2 selective inhibitor and the amount of corticotropin releasing factor antagonist) which will achieve the goal of improvement in disorder severity and the frequency of incidence over no treatment or treatment of each agent by itself.

[0074] The term "thrombotic event" or "thromboembolic event" includes, but is not limited to arterial thrombosis, including stent and graft thrombosis, cardiac thrombosis, coronary thrombosis, heart valve thrombosis, pulmonary thrombosis and venous thrombosis. Cardiac thrombosis is thrombosis in the heart. Pulmonary thrombosis is thrombosis in the lung. Arterial thrombosis is thrombosis in an artery. Coronary thrombosis is the development of an obstructive thrombus in a coronary artery, often causing sudden death or a myocardial infarction. Venous thrombosis is thrombosis in a vein. Heart valve thrombosis is a thrombosis on a heart valve. Stent thrombosis is thrombosis resulting from and/or located in the vicinity of a vascular stent. Graft thrombosis is thrombosis resulting from and/or located in the vicinity of an implanted graft, particularly a vascular graft. A thrombotic event as used herein is meant to embrace both a local thrombotic event and a distal thrombotic event occurring anywhere within the body (e.g., a thromboembolic event such as for example an embolic stroke).

[0075] The term "vaso-occlusive event" includes a partial occlusion (including a narrowing) or complete occlusion of a blood vessel, a stent or a vascular graft. A vaso-occlusive event intends to embrace thrombotic or thromboembolic events, and the vascular occlusion disorders or conditions to which they give rise. Thus, a vaso-occlusive event is intended to embrace all vascular occlusive disorders resulting in partial or total vessel occlusion from thrombotic or thromboembolic events.

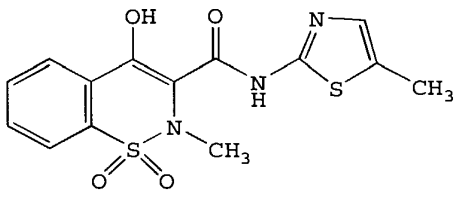
DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0076] The present invention provides a combination therapy comprising the administration to a subject of a therapeutically effective amount of a COX-2 selective inhibitor in combination with a therapeutically effective amount of a corticotropin releasing factor antagonist. The combination therapy is used to treat or prevent ischemic mediated central nervous system damage, such as damage to a central nervous system cell resulting from a decrease in blood flow to the cell or damage resulting from a traumatic injury to the cell. In addition, the combination therapy may

also be useful for the treatment of stroke or other vaso-occlusive events. When administered as part of a combination therapy, the COX-2 selective inhibitor together with the corticotropin releasing factor antagonist provide enhanced treatment options as compared to administration of the COX-2 selective inhibitor or the corticotropin releasing factor antagonist alone.

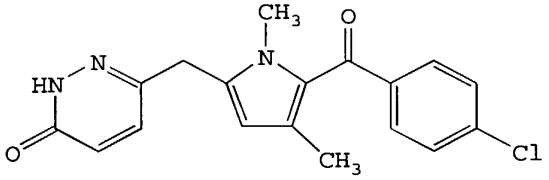
CYCLOOXYGENASE-2 SELECTIVE INHIBITORS

[0077] A number of suitable cyclooxygenase-2 selective inhibitors or isomers, pharmaceutically acceptable salts, esters, or prodrugs thereof, may be employed in the composition of the current invention. In one embodiment, the cyclooxygenase-2 selective inhibitor can be, for example, the cyclooxygenase-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-1.



B-1

[0078] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is the cyclooxygenase-2 selective inhibitor, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-2.

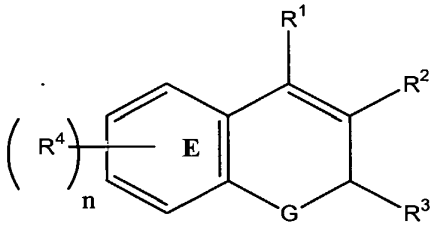


B-2

[0079] In still another embodiment the cyclooxygenase-2 selective inhibitor is a chromene compound that is a substituted benzopyran or a substituted benzopyran analog, and even more typically, selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, dihydronaphthalenes or a compound having

[0080] Formula *I* shown below and possessing, by way of example and not limitation, the structures disclosed in Table 1. Furthermore, benzopyran cyclooxygenase-2 selective inhibitors useful in the practice of the present methods are described in U.S. Patent No. 6,034,256 and 6,077,850 herein incorporated by reference in their entirety.

[0081] In another embodiment, the cyclooxygenase-2 selective inhibitor is a chromene compound represented by Formula *I* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(I)

[0082] wherein:

[0083] n is an integer which is 0, 1, 2, 3 or 4;

[0084] G is O, S or NR^a;

[0085] R^a is alkyl;

[0086] R^1 is selected from the group consisting of H and aryl;

[0087] R^2 is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[0088] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

[0089] each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0090] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0091] wherein:

[0092] n is an integer which is 0, 1, 2, 3 or 4;

[0093] G is O, S or NR^a;

[0094] R^a is alkyl;

[0095] R^1 is H;

[0096] R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[0097] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

[0098] each R^4 is independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0099] In a further embodiment, the cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)*, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0100] wherein:

[0101] n is an integer which is 0, 1, 2, 3 or 4;

[0102] G is oxygen or sulfur;

[0103] R^1 is H;

[0104] R^2 is carboxyl, lower alkyl, lower aralkyl or lower alkoxycarbonyl;

[0105] R^3 is lower haloalkyl, lower cycloalkyl or phenyl; and

[0106] each R^4 is independently H, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower

alkylcarbonyl; or R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0107] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0108] wherein:

[0109] n is an integer which is 0, 1, 2, 3 or 4;

[0110] G is oxygen or sulfur;

[0111] R^1 is H;

[0112] R^2 is carboxyl;

[0113] R^3 is lower haloalkyl; and

[0114] each R^4 is independently H, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0115] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0116] wherein:

[0117] n is an integer which is 0, 1, 2, 3 or 4;

[0118] G is oxygen or sulfur;

[0119] R^1 is H;

[0120] R^2 is carboxyl;

[0121] R^3 is fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, or trifluoromethyl; and

[0122] each R^4 is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-

methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0123] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0124] wherein:

[0125] n is an integer which is 0, 1, 2, 3 or 4;

[0126] G is oxygen or sulfur;

[0127] R^1 is H;

[0128] R^2 is carboxyl;

[0129] R^3 is trifluoromethyl or pentafluoroethyl; and

[0130] each R^4 is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0131] In yet another embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound having the structure of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0132] wherein:

[0133] n is 4;

[0134] G is O or S;

[0135] R^1 is H;

[0136] R^2 is CO_2H;

[0137] R^3 is lower haloalkyl;

[0138] a first R^4 corresponding to R^9 is hydrido or halo;

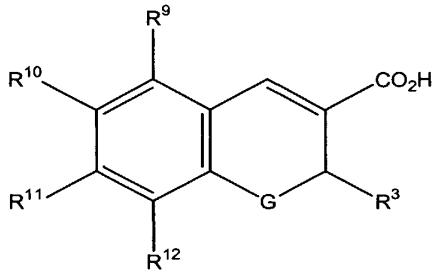
[0139] a second R^4 corresponding to R^{10} is H, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-

membered nitrogen-containing heterocyclosulfonyl, or 6- membered nitrogen-containing heterocyclosulfonyl;

[0140] a third R^4 corresponding to R^{11} is H, lower alkyl, halo, lower alkoxy, or aryl; and

[0141] a fourth R^4 corresponding to R^{12} is H, halo, lower alkyl, lower alkoxy, or aryl;

[0142] wherein Formula *(I)* is represented by Formula *(Ia)*:



(Ia)

[0143] The cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound of having the structure of Formula *(Ia)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0144] wherein:

[0145] G is O or S;

[0146] R^3 is trifluoromethyl or pentafluoroethyl;

[0147] R^9 is H, chloro, or fluoro;

[0148] R^{10} is H, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, or morpholinosulfonyl;

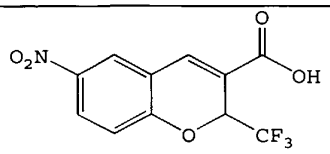
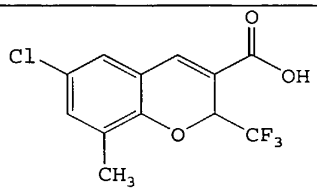
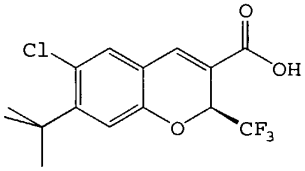
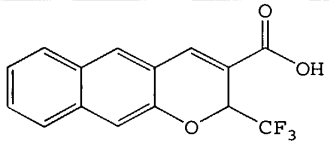
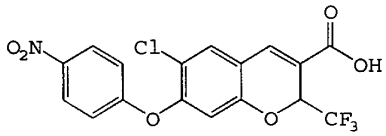
[0149] R^{11} is H, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, or phenyl; and

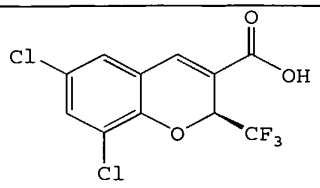
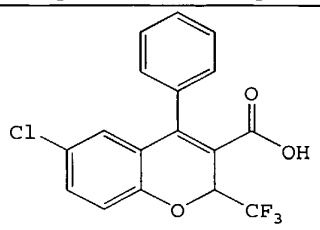
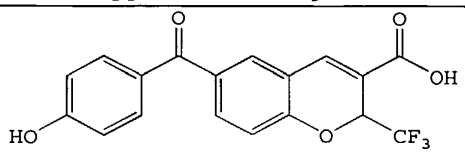
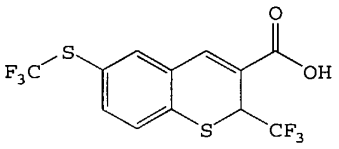
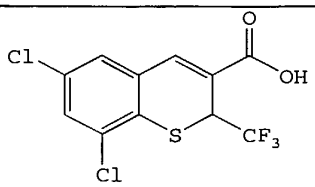
[0150] R^{12} is H, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, or phenyl.

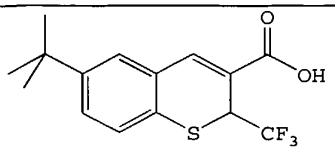
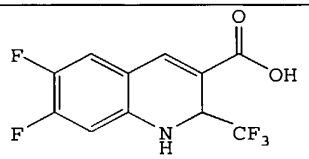
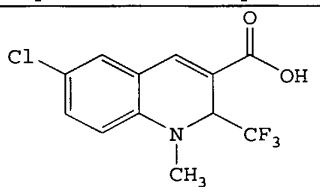
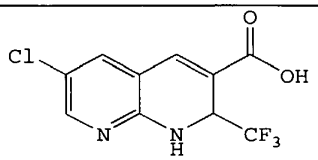
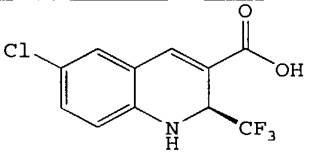
[0151] Examples of exemplary chromene cyclooxygenase-2 selective inhibitors are depicted in Table 1 below.

TABLE 1

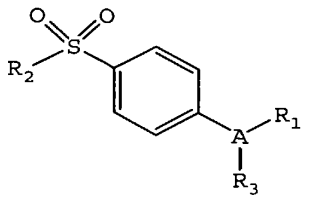
EXAMPLES OF CHROMENE CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1- benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl) -2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

[0152] In a further embodiment, the cyclooxygenase-2 selective inhibitor is selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of Formula *II* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,



II

[0153] wherein:

[0154] A is selected from the group consisting of a partially unsaturated or unsaturated heterocyclyl ring and a partially unsaturated or unsaturated carbocyclic ring;

[0155] R_1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R_1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[0156] R_2 is selected from the group consisting of methyl and amino; and

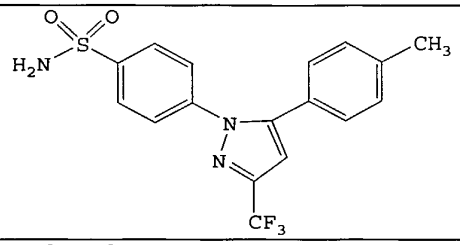
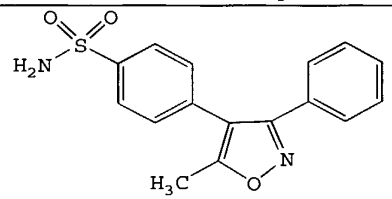
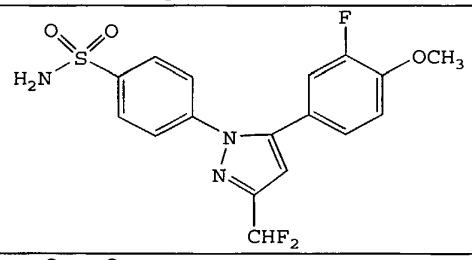
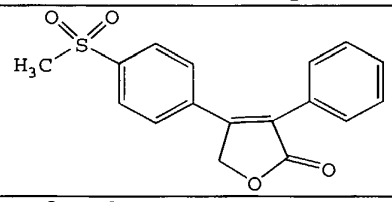
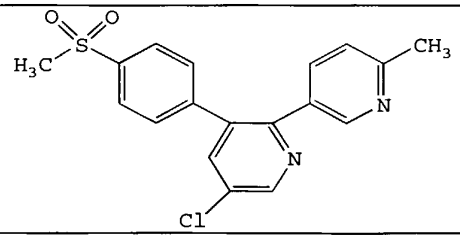
[0157] R_3 is selected from the group consisting of H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl.

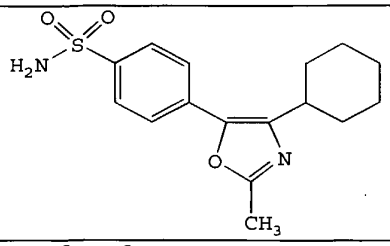
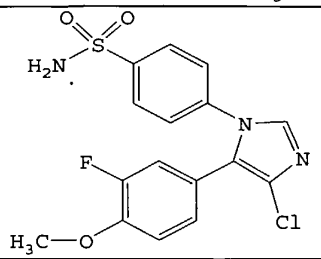
[0158] In another embodiment, the cyclooxygenase-2 selective inhibitor represented by the above Formula *II* is selected from the group of compounds illustrated in Table 2, consisting of celecoxib (B-18; U.S. Patent No. 5,466,823; CAS No. 169590-42-5), valdecoxib (B-19; U.S. Patent No. 5,633,272; CAS No. 181695-72-7),

deracoxib (B-20; U.S. Patent No. 5,521,207; CAS No. 169590-41-4), rofecoxib (B-21; CAS No. 162011-90-7), etoricoxib (MK-663; B-22; PCT publication WO 98/03484), tilmacoxib (JTE-522; B-23; CAS No. 180200-68-4), and cimicoxib (UR-8880; B23a; CAS No. 265114-23-6).

TABLE 2

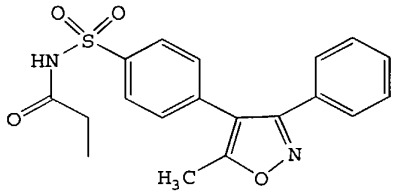
EXAMPLES OF TRICYCLIC CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

Compound Number	Structural Formula
B-18	
B-19	
B-20	
B-21	
B-22	

Compound Number	Structural Formula
B-23	
B23a	

[0159] In still another embodiment, the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

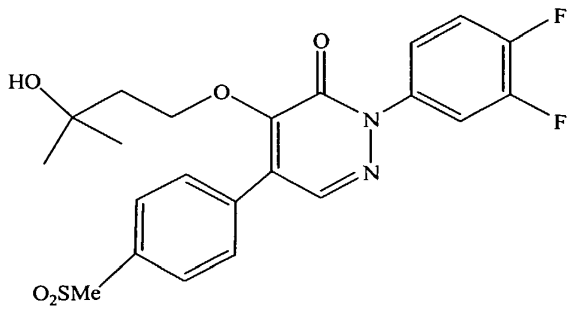
[0160] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is parecoxib (B-24, U.S. Patent No. 5,932,598, CAS No. 198470-84-7), which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, may be advantageously employed as a source of a cyclooxygenase inhibitor (US 5,932,598, herein incorporated by reference).



B-24

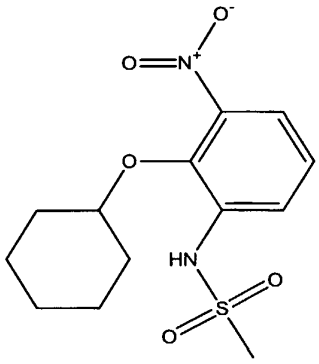
[0161] One form of parecoxib is sodium parecoxib.

[0162] In another embodiment of the invention, the compound having the formula B-25 or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-25 that has been previously described in International Publication number WO 00/24719 (which is herein incorporated by reference) is another tricyclic cyclooxygenase-2 selective inhibitor that may be advantageously employed.



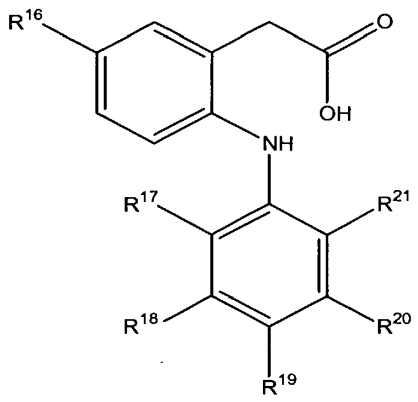
B-25

[0163] Another cyclooxygenase-2 selective inhibitor that is useful in connection with the method(s) of the present invention is N-(2-cyclohexyloxynitrophenyl)-methane sulfonamide (NS-398) having a structure shown below as B-26, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-26.



B-26

[0164] In yet a further embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula *(III)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(III)

[0165] wherein:

[0166] R^{16} is methyl or ethyl;

[0167] R^{17} is chloro or fluoro;

[0168] R^{18} is hydrogen or fluoro;

[0169] R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

[0170] R^{20} is hydrogen or fluoro; and

[0171] R^{21} is chloro, fluoro, trifluoromethyl or methyl, provided, however, that each of R^{17}, R^{18}, R^{20} and R^{21} is not fluoro when R^{16} is ethyl and R^{19} is H.

[0172] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention is a compound that has the designation of COX 189 (lumiracoxib; B-211) and that has the structure shown in Formula *(III)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

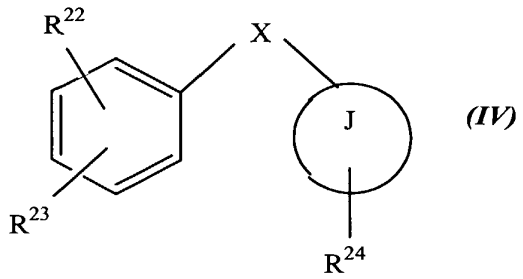
[0173] R^{16} is ethyl;

[0174] R^{17} and R^{19} are chloro;

[0175] R^{18} and R^{20} are hydrogen; and

[0176] R^{21} is methyl.

[0177] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is represented by Formula *(IV)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(IV)

[0178] wherein:

[0179] X is O or S;

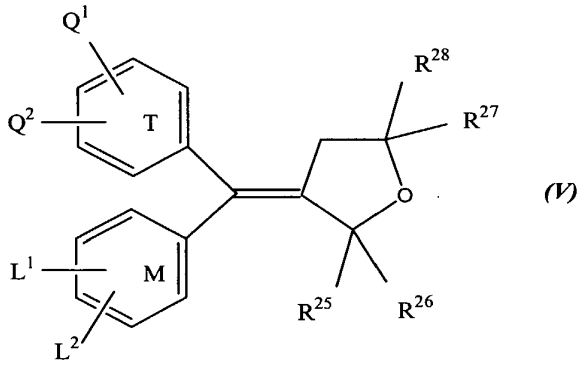
[0180] J is a carbocycle or a heterocycle;

[0181] R^{22} is $NHSO_2CH_3$ or F;

[0182] R^{23} is H, NO_2, or F; and

[0183] R^{24} is H, $NHSO_2CH_3$, or $(SO_2CH_3)C_6H_4$.

[0184] According to another embodiment, the cyclooxygenase-2 selective inhibitors used in the present method(s) have the structural Formula *(V)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(V)

[0185] wherein:

[0186] T and M are independently phenyl, naphthyl, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

[0187] R^{25}, R^{26}, R^{27}, and R^{28} are independently hydrogen, halogen, lower alkyl radical having from 1 to 6 carbon atoms, lower haloalkyl radical having from 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or

[0188] R^{25} and R^{26}, together with the carbon atom to which they are attached, form a carbonyl or a saturated hydrocarbon ring having from 3 to 7 carbon atoms; or

[0189] $R^{27}$and R^{28}, together with the carbon atom to which they are attached, form a carbonyl or a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

[0190] Q^1, Q^2, L^1 or L^2 are independently hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, trifluoromethyl, lower methoxy having from 1 to 6 carbon atoms, alkylsulfinyl or alkylsulfonyl; and

[0191] at least one of Q^1, Q^2, L^1 or L^2 is in the para position and is $-S(O)_n-R$, wherein n is 0, 1, or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having from 1 to 6 carbon atoms, or an $-SO_2NH_2$; or Q^1 and Q^2 together form methylenedioxy; or L^1 and L^2 together form methylenedioxy.

[0192] In another embodiment, the compounds N-(2-cyclohexyloxynitrophenyl) methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide or isomers, pharmaceutically acceptable salts, esters, or prodrugs thereof having the structure of Formula *(V)* are employed as cyclooxygenase-2 selective inhibitors.

[0193] In a further embodiment, compounds that are useful for the cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof used in connection with the method(s) of the present invention, the structures for which are set forth in Table 3 below, include, but are not limited to:

[0194] 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-27);

[0195] 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-28);

[0196] 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-29);

[0197] 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-30);

[0198] 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid (B-31);

[0199] 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-32);

[0200] 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-33);

[0201] 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-34);

[0202] 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-35);

[0203] 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-36);

[0204] 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-37);

[0205] 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-38);

[0206] 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-39);

[0207] 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-40);

[0208] 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-41);

[0209] 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-42);

[0210] 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-43);

[0211] 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-44);

[0212] 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-45);

[0213] 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-46);

[0214] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-47);

[0215] 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-48)

[0216] 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-49);

[0217] 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-50);

[0218] 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-51);

[0219] 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-52);

[0220] 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-53);

[0221] 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-54);

[0222] 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-55);

[0223] 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-56);

[0224] 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-57);

[0225] 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-58);

[0226] 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-59);

[0227] 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-60);

[0228] 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-61);

[0229] 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-62);

[0230] 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-63);

[0231] 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-64);

[0232] 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-65);

[0233] 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-66);

[0234] 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-67);

[0235] 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-68);

[0236] 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-69);

[0237] 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-70);

[0238] 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-71);

[0239] 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid (B-72);

[0240] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-73);

[0241] 3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one or BMS-347070 (B-74);

[0242] 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a) pyridine (B-75);

[0243] 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone (B-76);

[0244] 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (B-77);

[0245] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole (B-78);

[0246] 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-79);

[0247] 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-80);

[0248] 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl) benzenesulfonamide (B-81);

[0249] 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-82);

[0250] 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-83);

[0251] 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-84);

[0252] 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-85);

[0253] 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-86);

[0254] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-87);

[0255] 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-88);

[0256] 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-89);

[0257] 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-90);

[0258] 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-91);

[0259] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-92);

[0260] 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-93);

[0261] 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-94);

[0262] 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl] benzenesulfonamide (B-95);

[0263] 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-96);

[0264] 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-97);

[0265] 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-98);

[0266] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-99);

[0267] 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-100);

[0268] 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-101);

[0269] 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-102);

[0270] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-

[0271] 5-ene (B-103);

[0272] 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-104);

[0273] 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-

[0274] 6-ene (B-105);

[0275] 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl) phenyl]spiro [2.4]hept-5-ene (B-106);

[0276] 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-107);

[0277] 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro [2.4]hept-5-ene (B-108);

[0278] 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl] spiro[2.4]hept-5-ene (B-109);

[0279] 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-110);

[0280] 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonyl phenyl)thiazole (B-111);

[0281] 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonyl phenyl)thiazole (B-112);

[0282] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole (B-113);

[0283] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-114);

[0284] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole (B-115);

[0285] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole (B-116);

[0286] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino) thiazole (B-117);

[0287] 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methyl sulfonyl)phenyl]thiazole (B-118);

[0288] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-119);

[0289] 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene (B-120);

[0290] 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl] benzenesulfonamide (B-121);

[0291] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene (B-122);

[0292] 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl] benzenesulfonamide (B-123);

[0293] 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-124);

[0294] 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-125);

[0295] 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile (B-126);

[0296] 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-127);

[0297] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-128);

[0298] 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-129);

[0299] 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl] pyridine (B-130);

[0300] 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-

[0301] 2-yl]pyridine (B-131);

[0302] 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-132);

[0303] 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-133);

[0304] 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-134);

[0305] 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-135);

[0306] 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-136);

[0307] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole (B-137);

[0308] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole (B-138);

[0309] 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (B-139);

[0310] 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoro methyl)-1H-imidazole (B-140);

[0311] 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole (B-141);

[0312] 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-142);

[0313] 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-143);

[0314] 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoro methyl)-1H-imidazole (B-144);

[0315] 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-145);

[0316] 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-146);

[0317] 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzene sulfonamide (B-147);

[0318] 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole (B-148);

[0319] 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-149);

[0320] 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-150);

[0321] 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-151);

[0322] 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoro methyl)-1H-pyrazole (B-152);

[0323] 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide (B-153);

[0324] N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide (B-154);

[0325] ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate (B-155);

[0326] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole (B-156);

[0327] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole (B-157);

[0328] 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-158);

[0329] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole (B-159);

[0330] 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole (B-160);

[0331] 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-161);

[0332] 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-162);

[0333] 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine (B-163);

[0334] 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-164);

[0335] 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide (B-165);

[0336] 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene (B-166);

[0337] 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole (B-167);

[0338] 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide (B-168);

[0339] 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-169);

[0340] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-170);

[0341] 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide (B-171);

[0342] 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-172);

[0343] 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-173);

[0344] 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-174);

[0345] 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-175);

[0346] 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-176);

[0347] 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methyl sulfonyl)benzene (B-177);

[0348] 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-178);

[0349] 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzene sulfonamide (B-179);

[0350] 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-180);

[0351] 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzene sulfonamide (B-181);

[0352] 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-182);

[0353] 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-183);

[0354] 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-184);

[0355] 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-185);

[0356] 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl] benzenesulfonamide (B-186);

[0357] 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-187);

[0358] 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl] benzenesulfonamide (B-188);

[0359] 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide (B-189);

[0360] ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate (B-190);

[0361] 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl] acetic acid (B-191);

[0362] 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] oxazole (B-192);

[0363] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole (B-193);

[0364] 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole (B-194);

[0365] 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl] benzenesulfonamide (B-195);

[0366] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-196);

[0367] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-197);

[0368] 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone (B-198);

[0369] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-199);

[0370] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide (B-200);

[0371] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide (B-201);

[0372] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-202);

[0373] 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-203);

[0374] 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-204);

[0375] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-205);

[0376] 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-206);

[0377] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-207);

[0378] [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl] benzenesulfonamide (B-208);

[0379] 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide (B-209);

[0380] 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl] benzenesulfonamide (B-210);

[0381] [2-(2-chloro-6-fluoro-phenylamino)-5-methyl-phenyl]-acetic acid or COX 189 (lumiracoxib; B-211);

[0382] N-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or nimesulide (B-212);

[0383] N-[6-(2,4-difluoro-phenoxy)-1-oxo-indan-5-yl]-methanesulfonamide or flosulide (B-213);

[0384] N-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1H-inden-5-yl]-methanesulfonamide, sodium salt (B-214);

[0385] N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide (B-215);

[0386] 3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5H-furan-2-one (B-216);

[0387] (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl] methylene]-4(5H)-thiazolone (B-217);

[0388] CS-502 (B-218);

[0389] LAS-34475 (B-219);

[0390] LAS-34555 (B-220);

[0391] S-33516 (B-221);

[0392] SD-8381 (B-222);

[0393] L-783003 (B-223);

[0394] N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide (B-224);

[0395] D-1367 (B-225);

[0396] L-748731 (B-226);

[0397] (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid (B-227);

[0398] CGP-28238 (B-228);

[0399] 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389 (B-229);

[0400] GR-253035 (B-230);

[0401] 6-dioxo-9H-purin-8-yl-cinnamic acid (B-231);

[0402] S-2474 (B-232);

[0403] 4-[4-(methyl)-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone;

[0404] 4-(5-methyl-3-phenyl-4-isoxazolyl);

[0405] 2-(6-methylpyrid-3-yl)-3-(4-methylsulfonylphenyl)-5-chloropyridine;

[0406] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl];

[0407] N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl];

[0408] 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-

[0409] 1-yl]benzenesulfonamide;

[0410] (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;

[0411] 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methyl sulfonyl)phenyl]-3(2H)-pyridzainone;

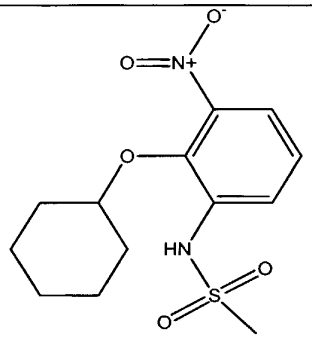
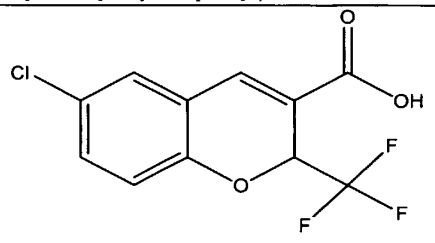
[0412] 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

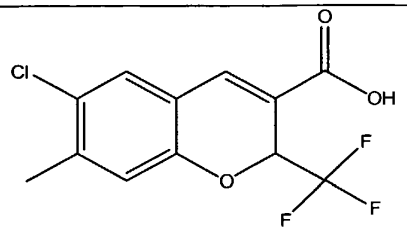
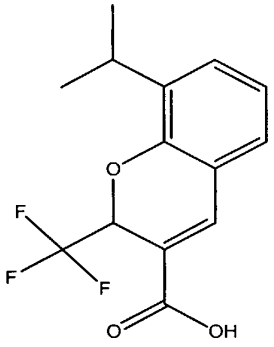
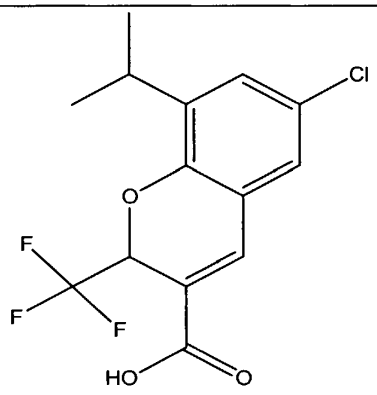
[0413] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

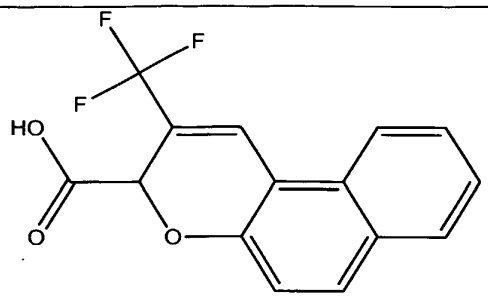
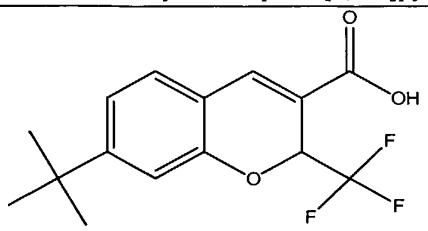
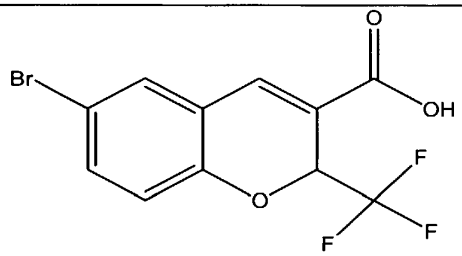
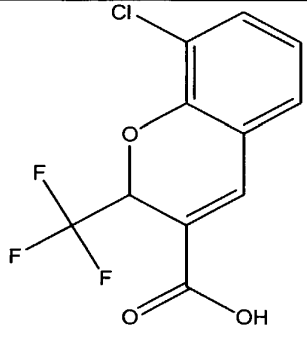
[0414] [2-(2,4-dichloro-6-ethyl-3,5-dimethyl-phenylamino)-5-propyl-phenyl]-acetic acid.

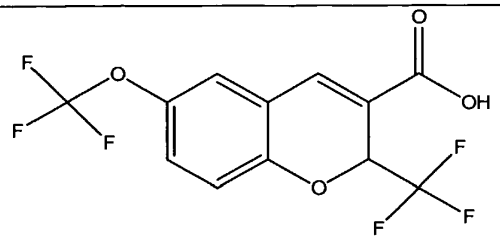
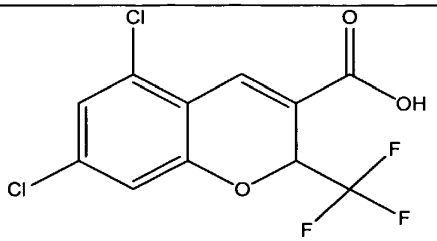
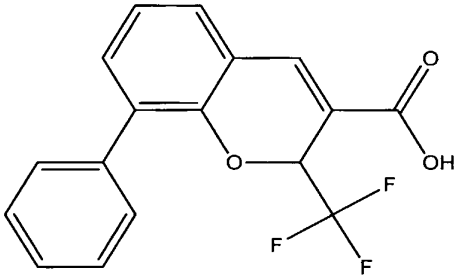
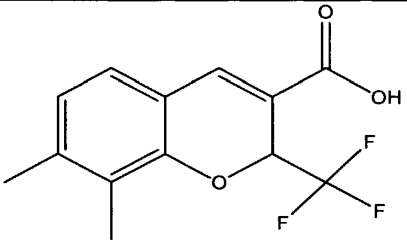
TABLE 3

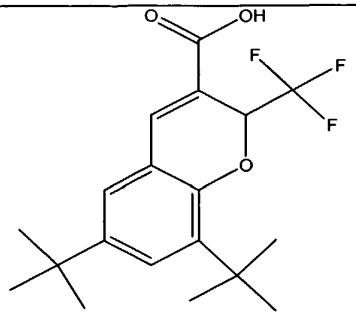
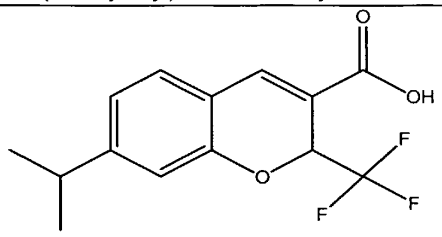
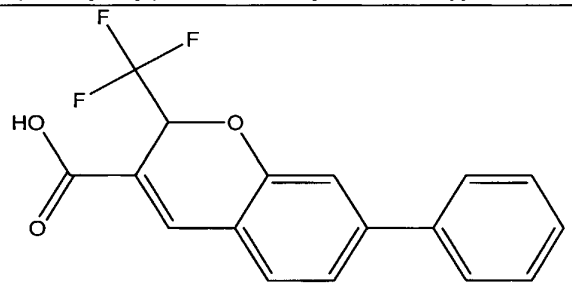
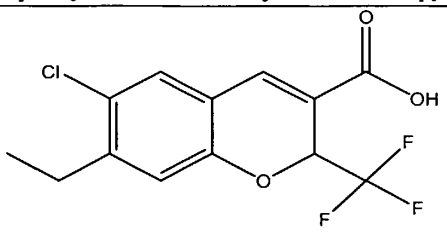
EXAMPLES OF CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

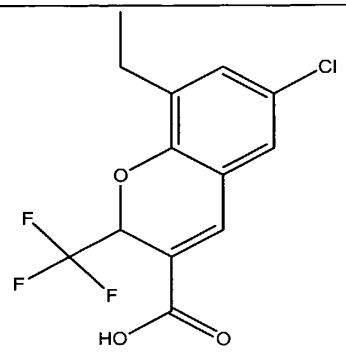
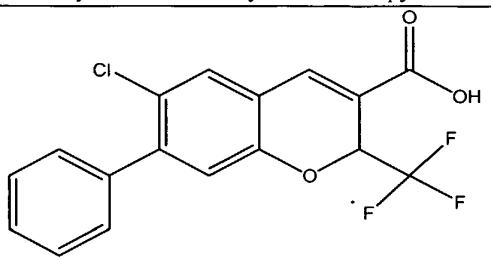
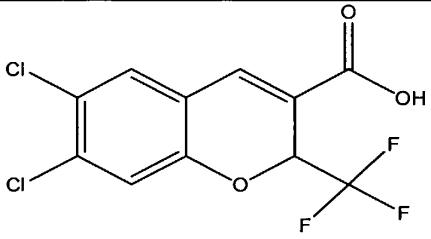
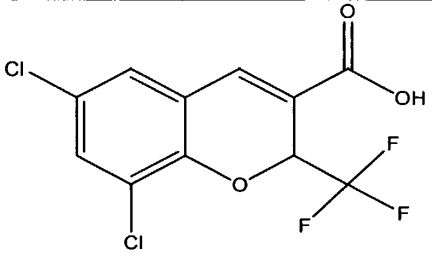
Compound Number	**Structural Formula**
B-26	 N-(2-cyclohexyloxynitrophenyl) methane sulfonamide or NS-398;
B-27	 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

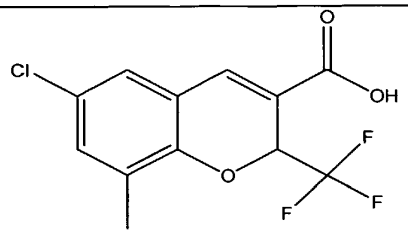
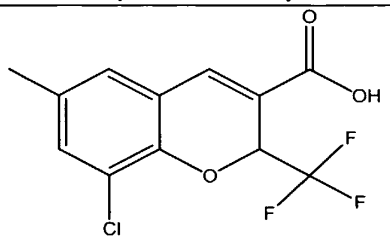
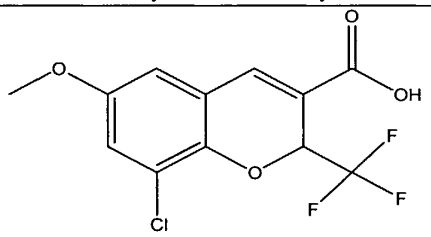
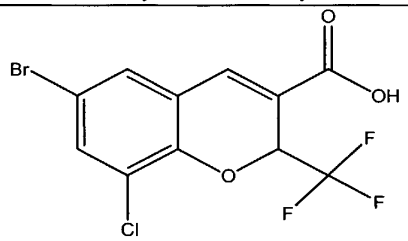
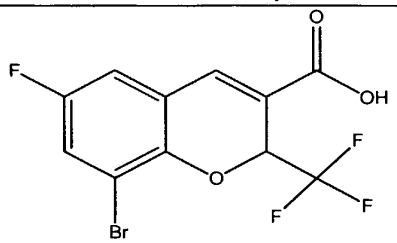
Compound Number	Structural Formula
B-28	 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-29	 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-30	 6-chloro-8-(1-methylethyl)-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;

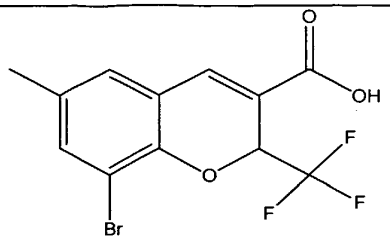
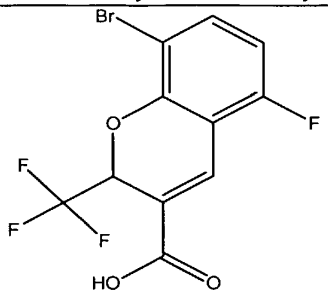
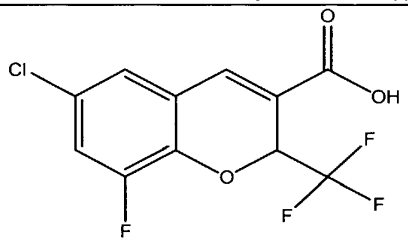
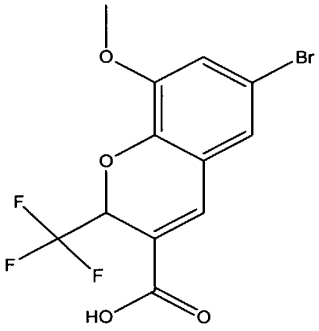
Compound Number	Structural Formula
B-31	 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;
B-32	 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-33	 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-34	 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

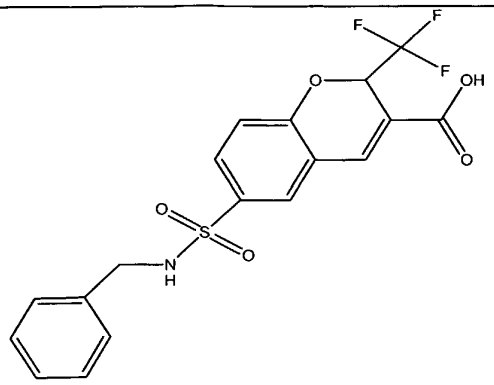
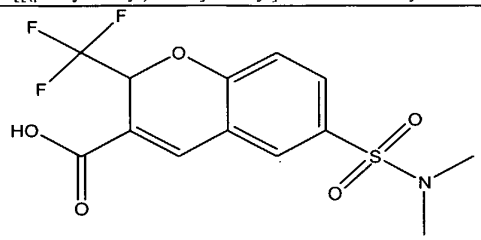
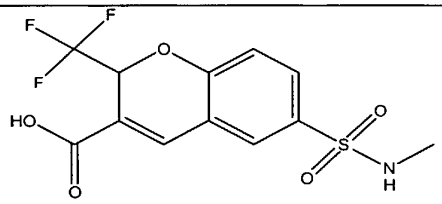
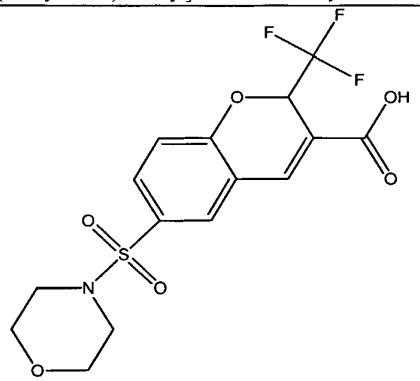
Compound Number	Structural Formula
B-35	 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-36	 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-37	 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-38	 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

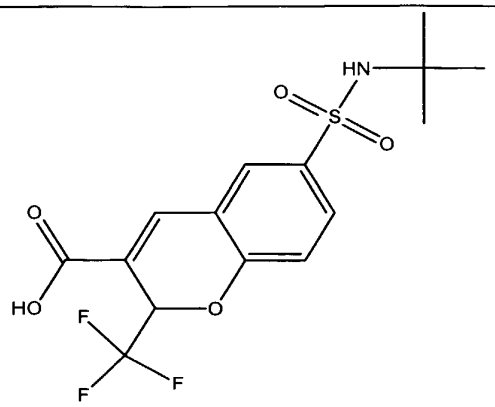
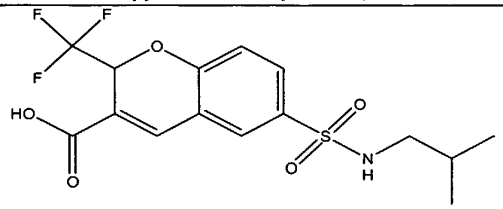
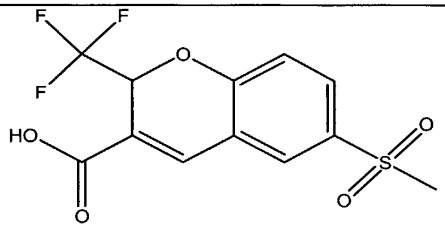
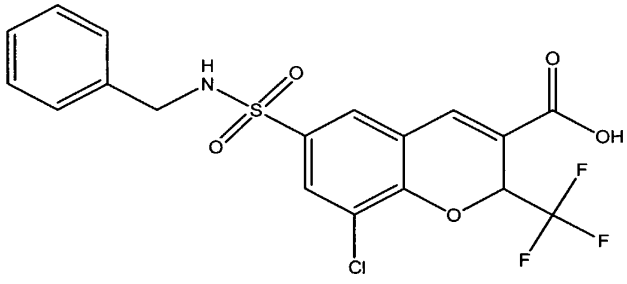
Compound Number	Structural Formula
B-39	 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-40	 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-41	 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-42	 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

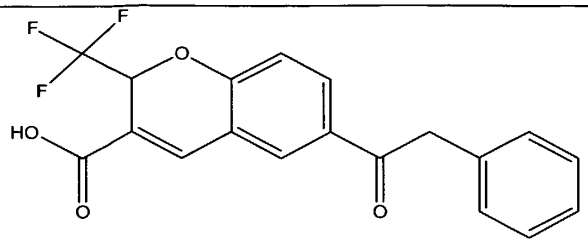
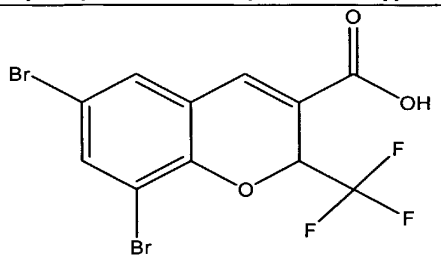
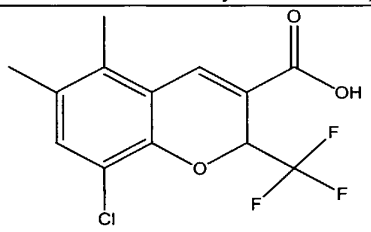
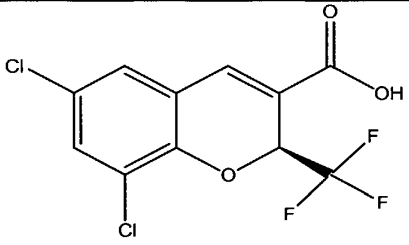
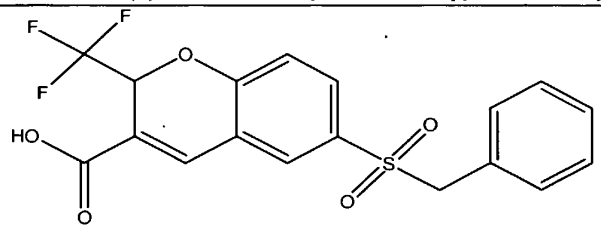
Compound Number	Structural Formula
B-43	 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-44	 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-45	 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-46	 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

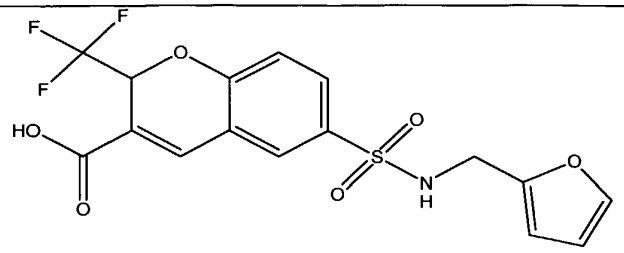
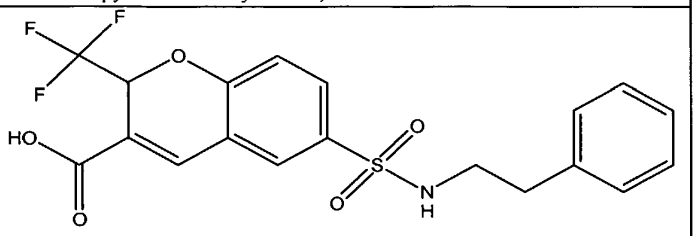
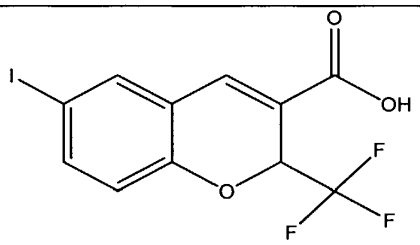
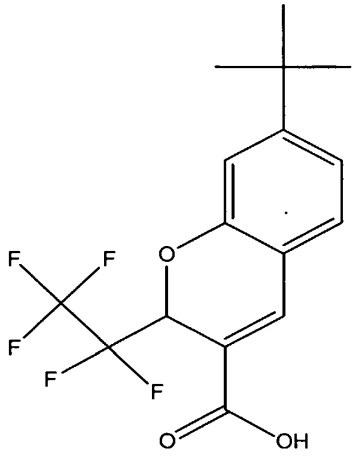
Compound Number	Structural Formula
B-47	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-48	 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-49	 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-50	 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-51	 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

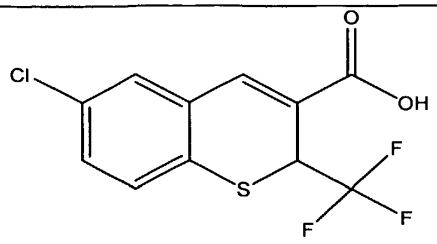
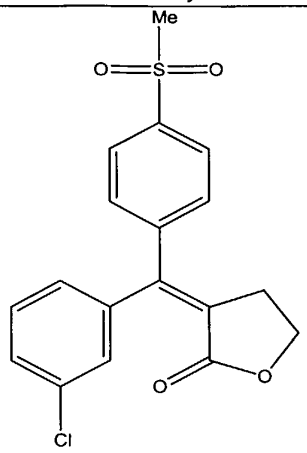
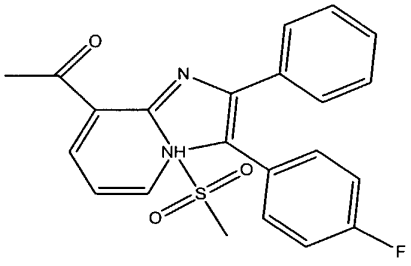
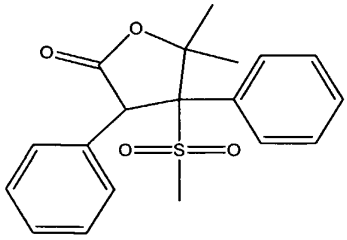
Compound Number	Structural Formula
B-52	 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-53	 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-54	 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-55	 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

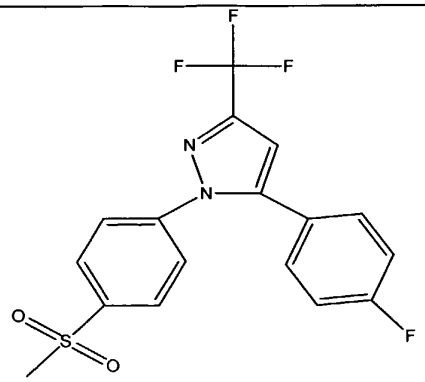
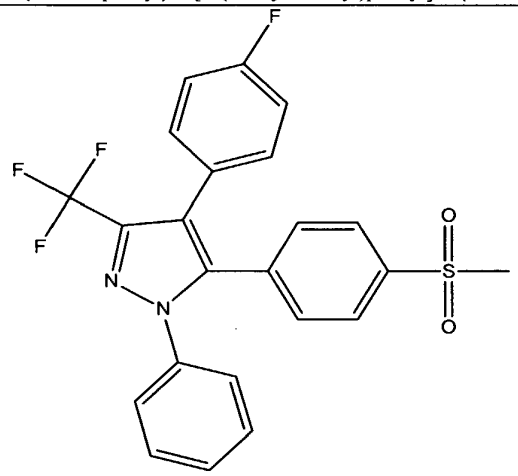
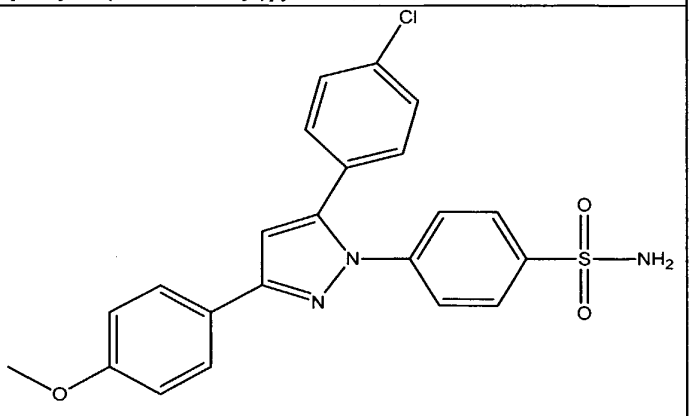
Compound Number	Structural Formula
B-56	 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-57	 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-58	 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-59	 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

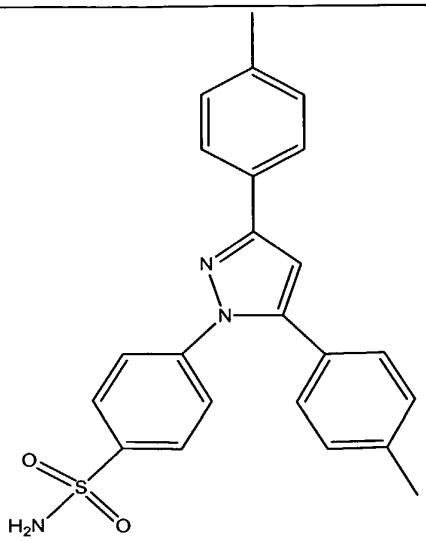
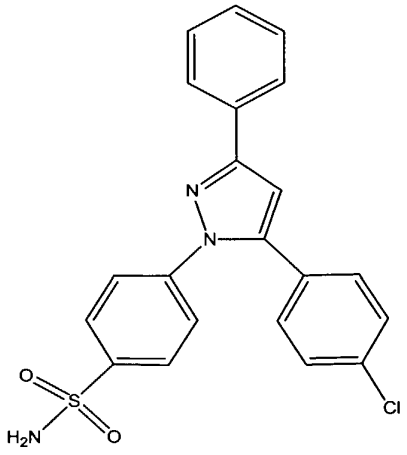
Compound Number	Structural Formula
B-60	 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-61	 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-62	 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-63	 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl- 2H-1-benzopyran-3-carboxylic acid;

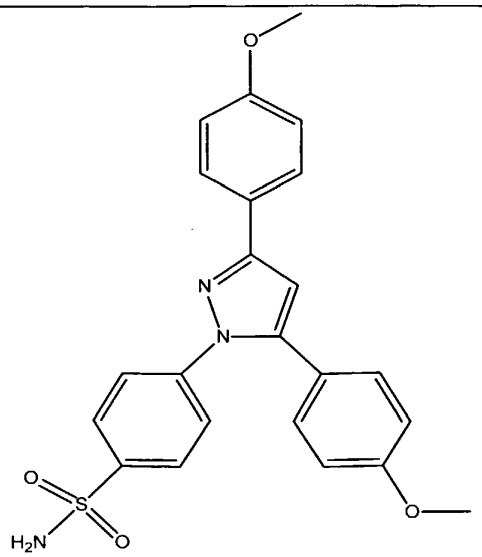
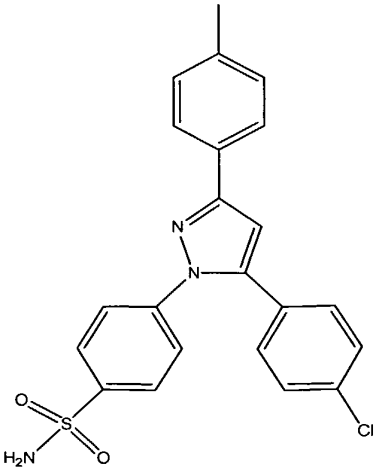
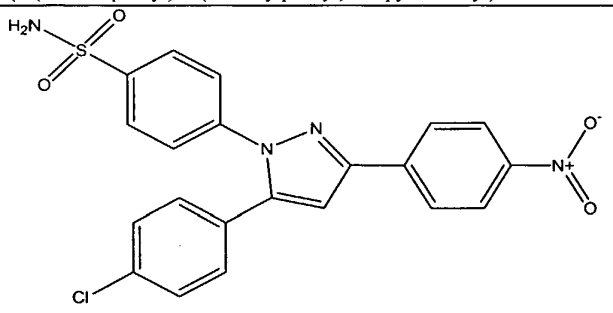
Compound Number	Structural Formula
B-64	 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-65	 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-66	 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-67	 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-68	 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

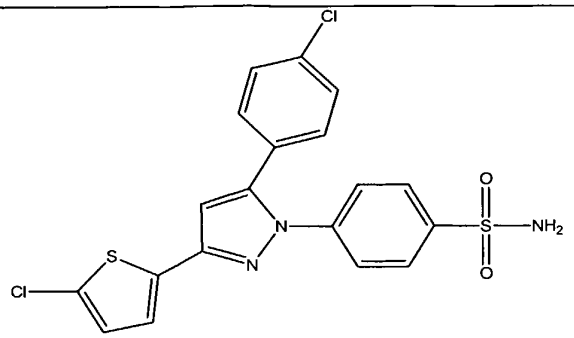
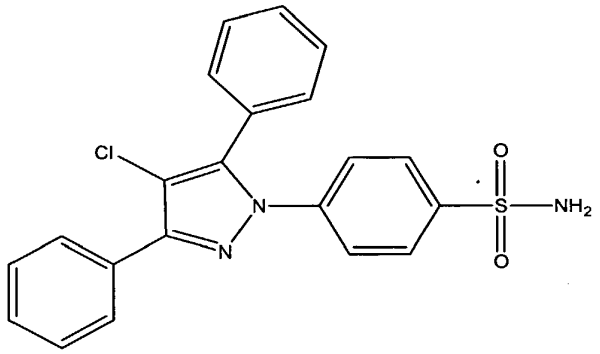
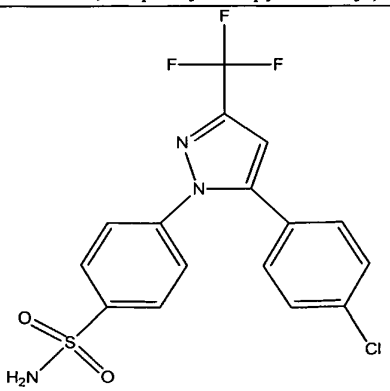
Compound Number	Structural Formula
B-69	 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-70	 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran -3-carboxylic acid;
B-71	 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-72	 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H -1-benzopyran-3-carboxylic acid;

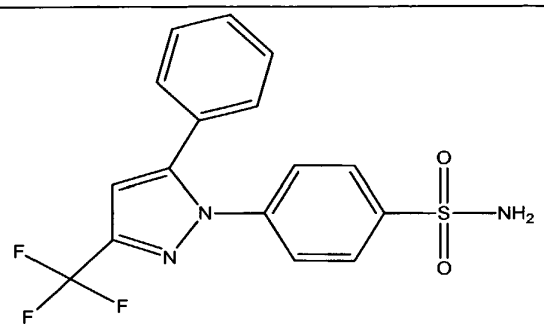
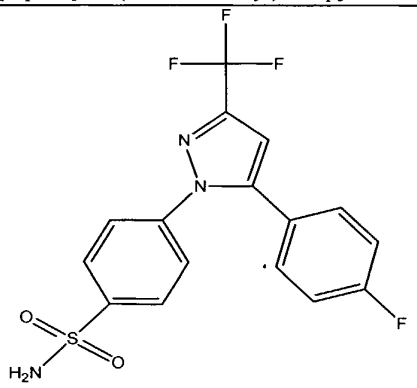
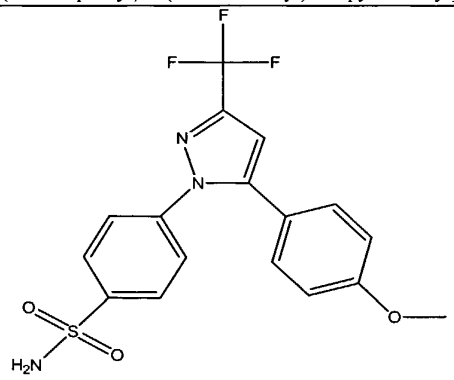
Compound Number	Structural Formula
B-73	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
B-74	 3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene] -dihydro-furan-2-one or BMS-347070;
B-75	 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;
B-76	 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

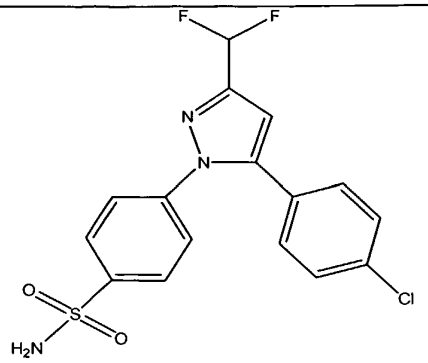
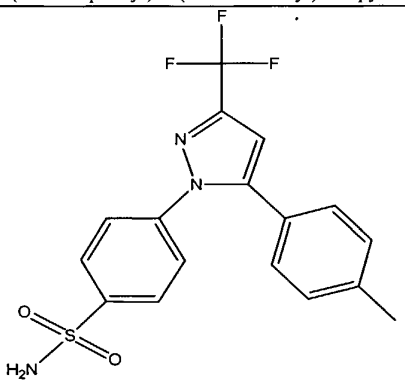
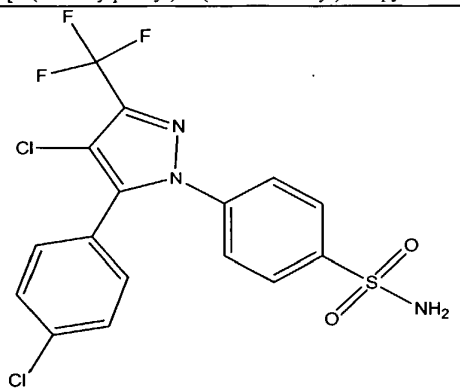
Compound Number	Structural Formula
B-77	 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;
B-78	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -1-phenyl-3-(trifluoromethyl)pyrazole;
B-79	 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide;

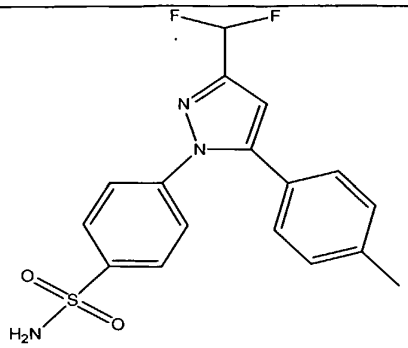
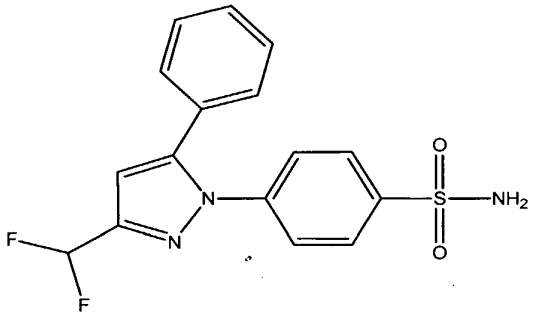
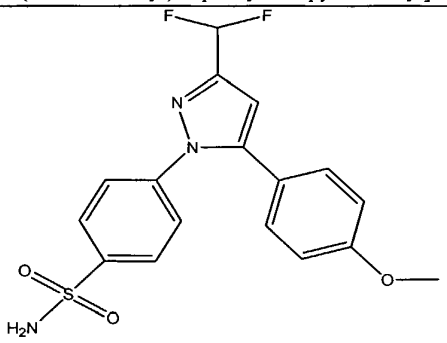
Compound Number	Structural Formula
B-80	 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-81	 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

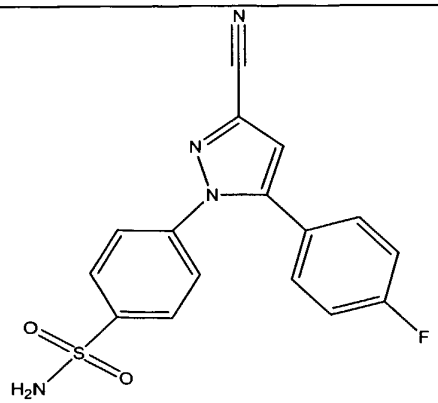
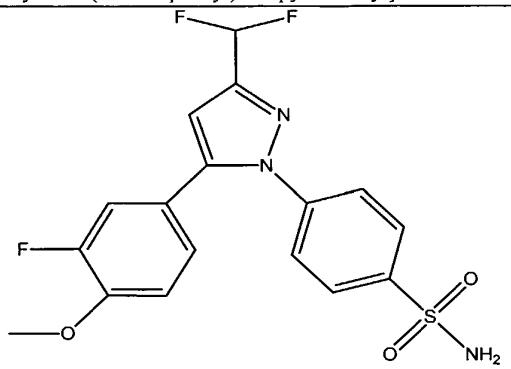
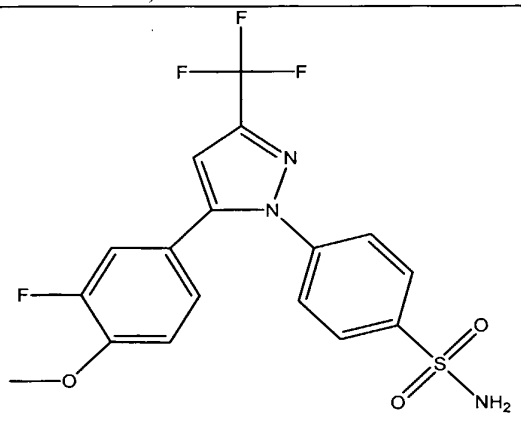
Compound Number	Structural Formula
B-82	 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-83	 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-84	 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

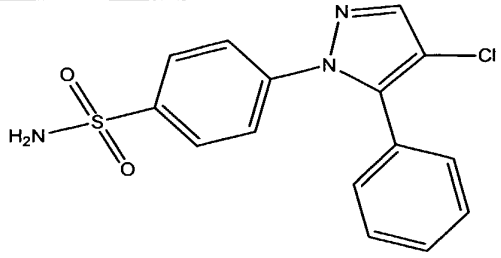
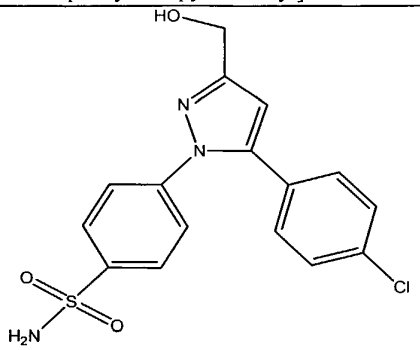
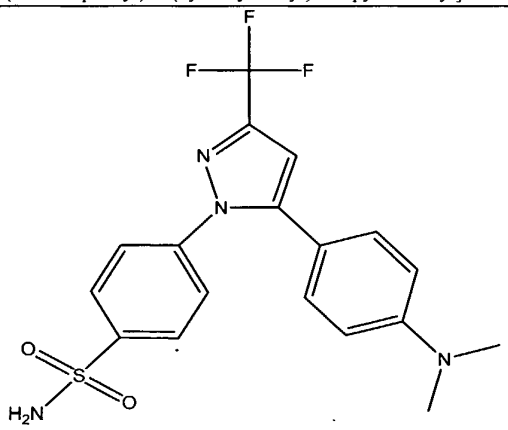
Compound Number	Structural Formula
B-85	 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-86	 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;
B-87	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

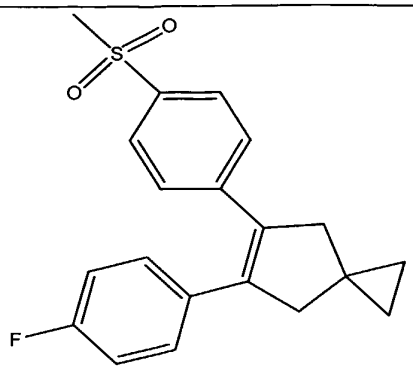
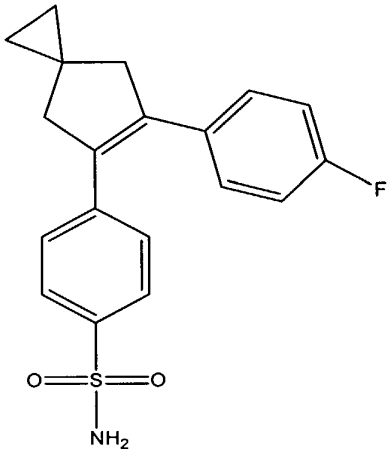
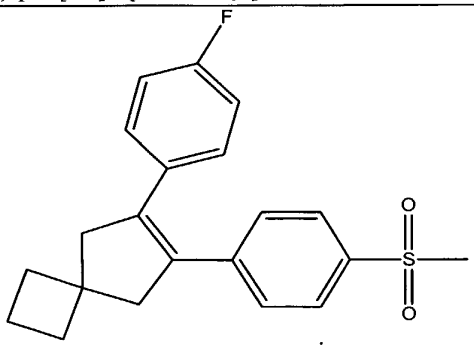
Compound Number	Structural Formula
B-88	 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-89	 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-90	 4[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

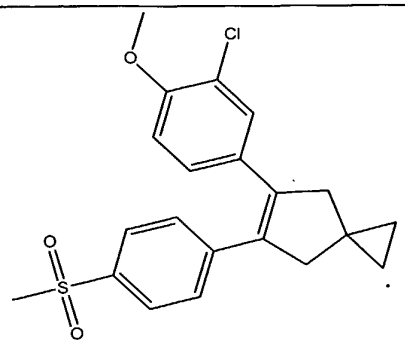
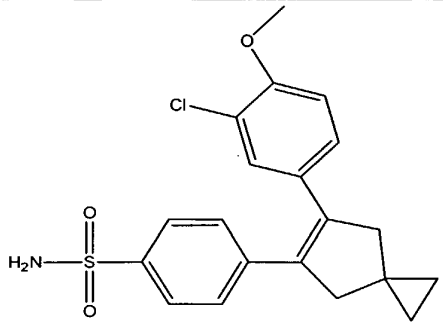
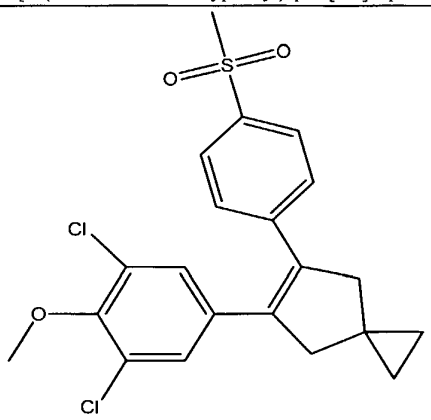
Compound Number	Structural Formula
B-91	 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-92	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-93	 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

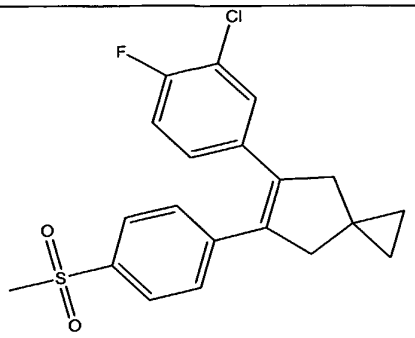
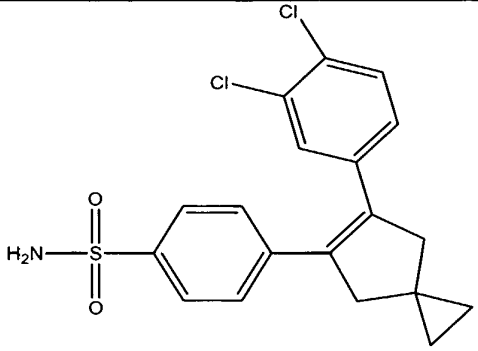
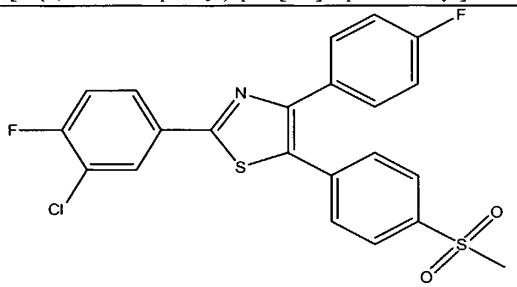
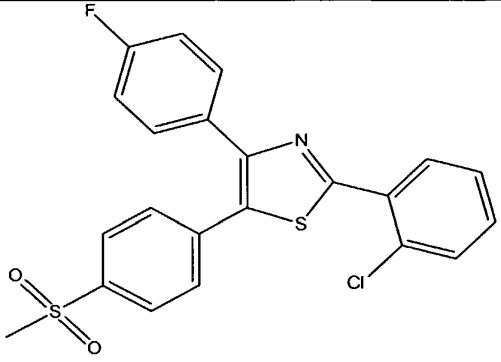
Compound Number	Structural Formula
B-94	 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-95	 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-96	 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

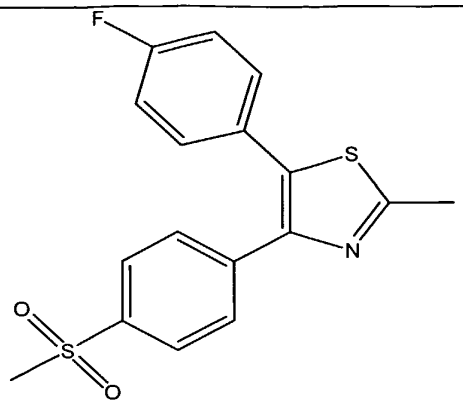
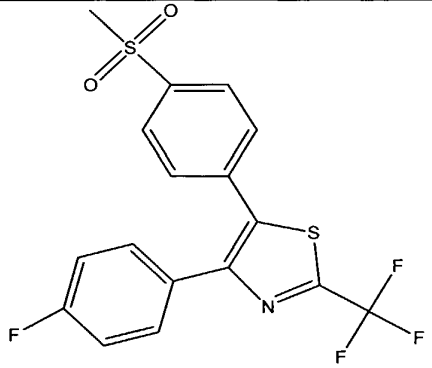
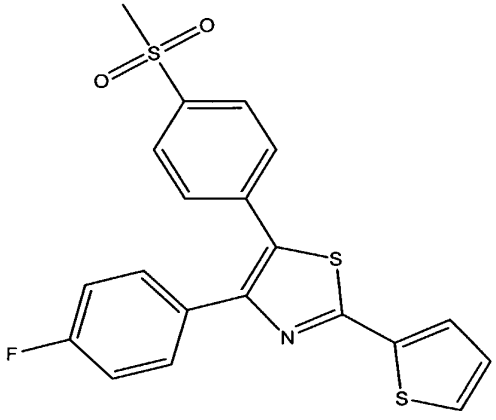
Compound Number	Structural Formula
B-97	 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-98	 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide;
B-99	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

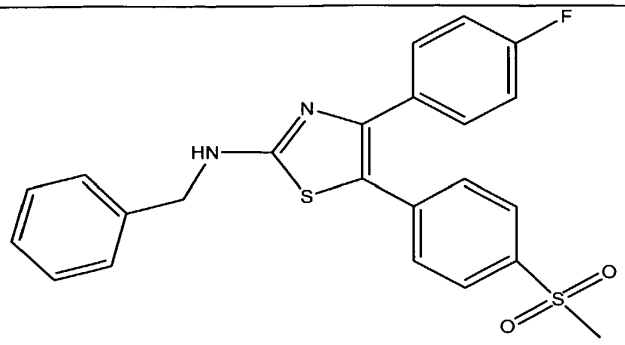
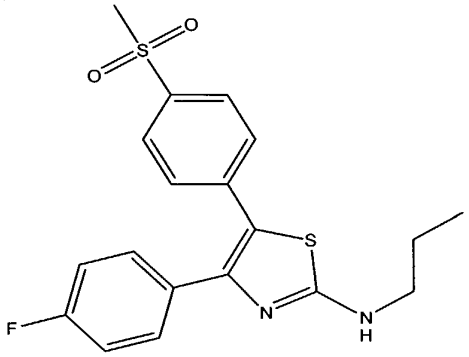
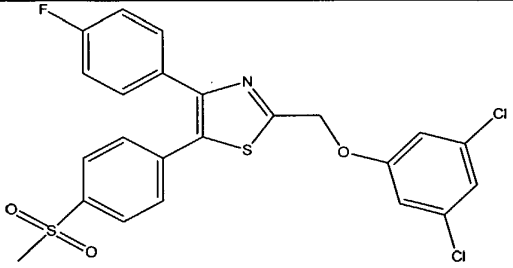
Compound Number	Structural Formula
B-100	 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-101	 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-102	 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide;

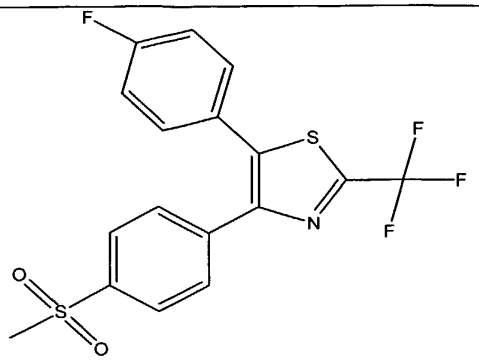
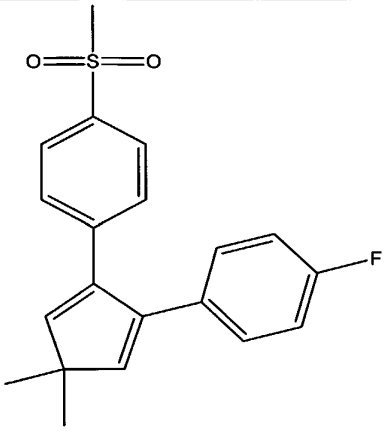
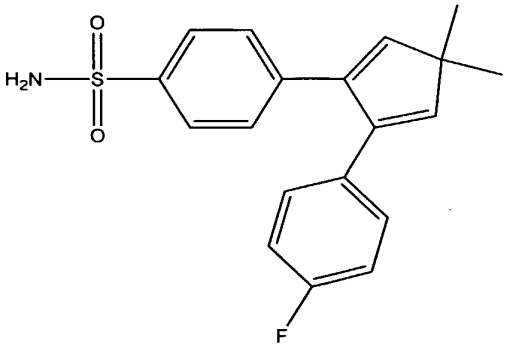
Compound Number	Structural Formula
B-103	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-104	 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-105	 6-(4-fluorophenyl)-7-[4-methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

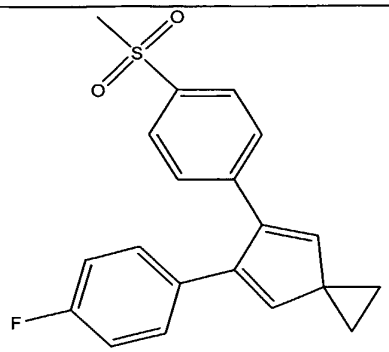
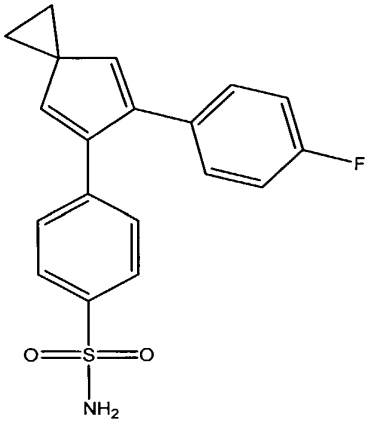
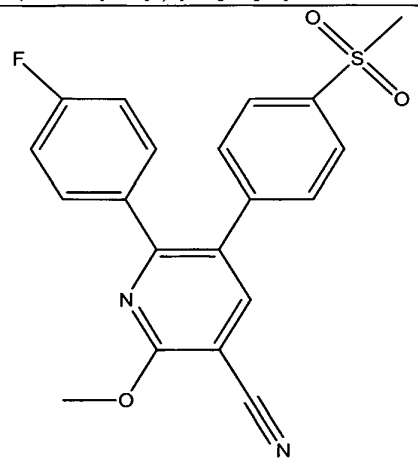
Compound Number	Structural Formula
B-106	 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-107	 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-108	 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl] spiro[2.4]hept-5-ene;

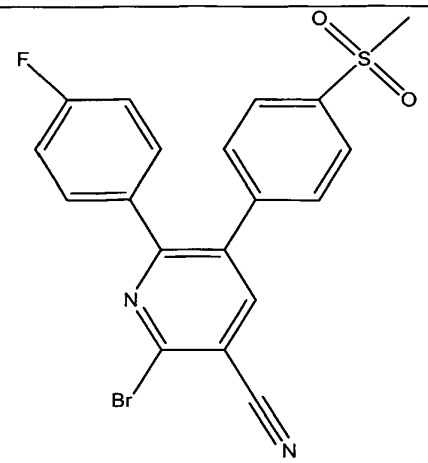
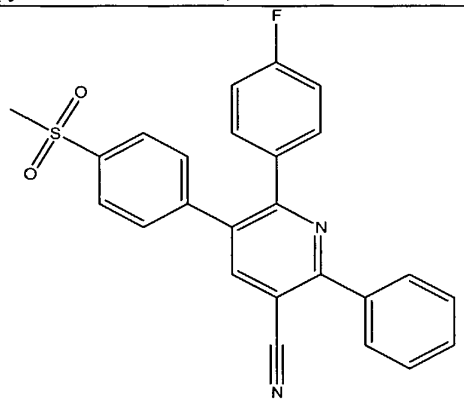
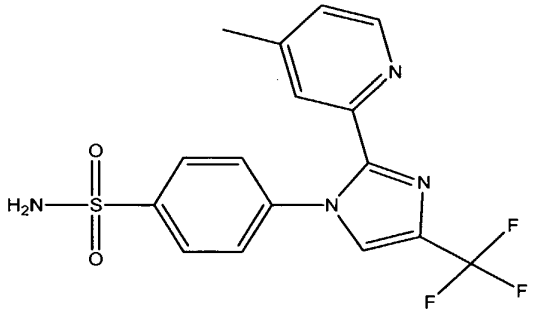
Compound Number	Structural Formula
B-109	 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-110	 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-111	 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
B-112	 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

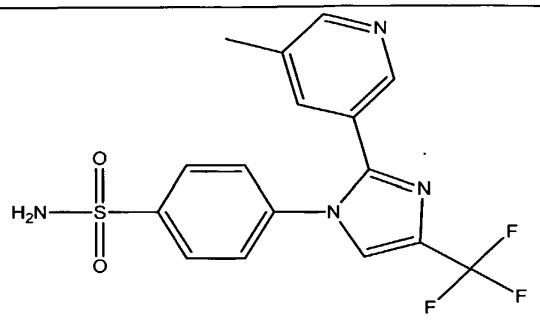
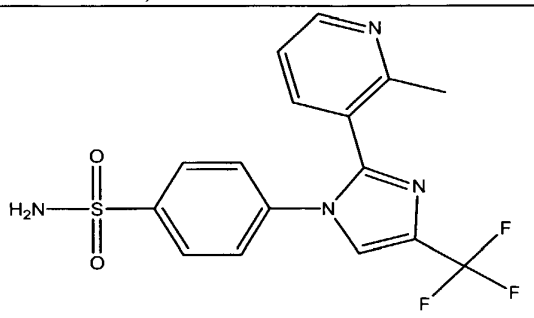
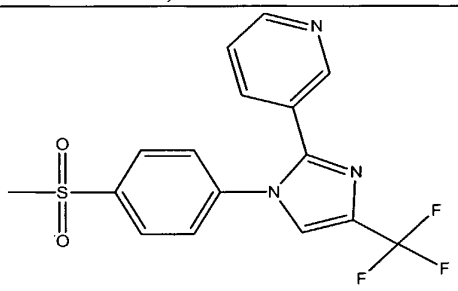
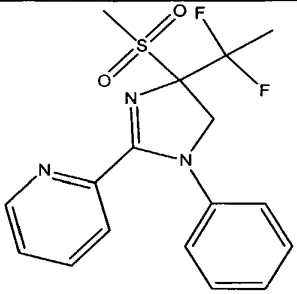
Compound Number	Structural Formula
B-113	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
B-114	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
B-115	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

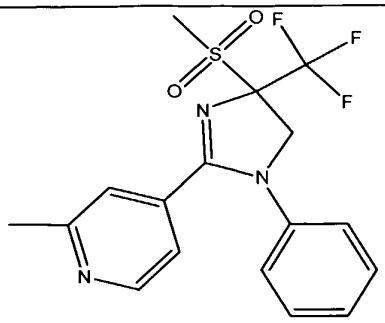
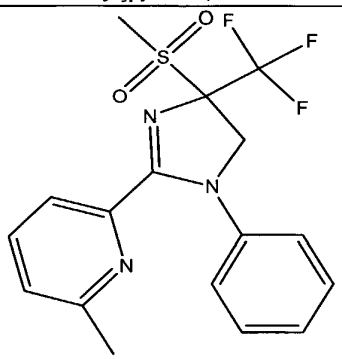
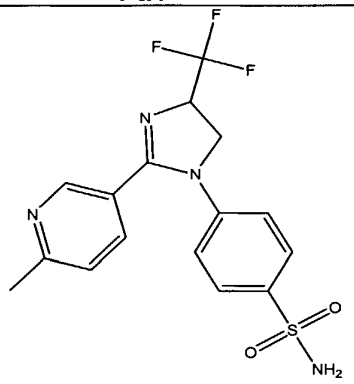
Compound Number	Structural Formula
B-116	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
B-117	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
B-118	 2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

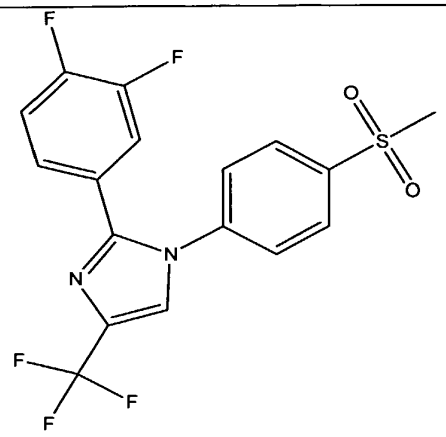
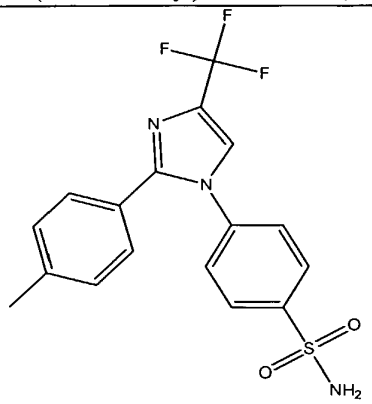
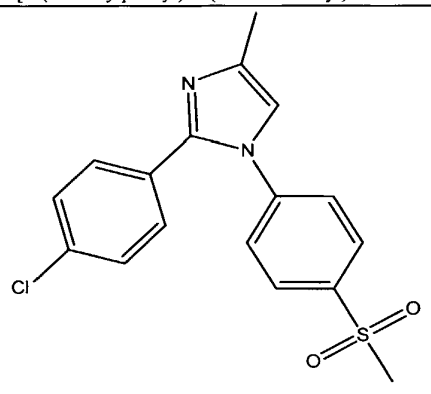
Compound Number	Structural Formula
B-119	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
B-120	 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl) cyclopenta-2,4-dien-3-yl]benzene;
B-121	 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl] benzenesulfonamide;

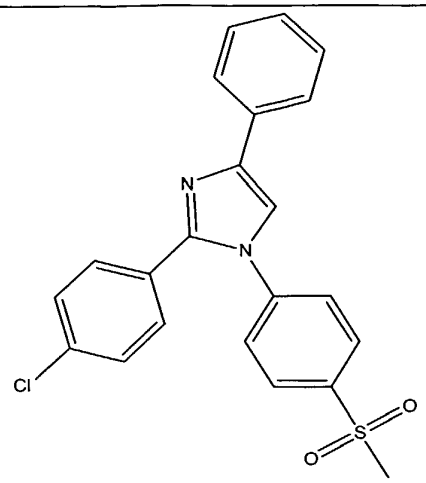
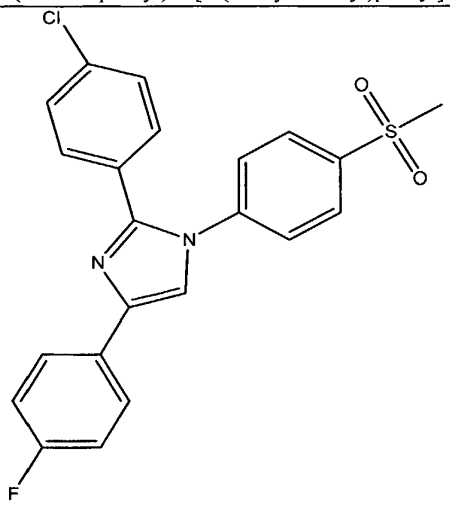
Compound Number	Structural Formula
B-122	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
B-123	 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;
B-124	 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile;

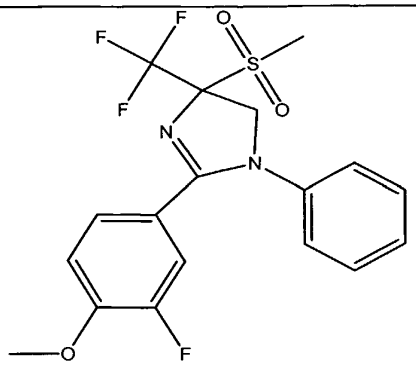
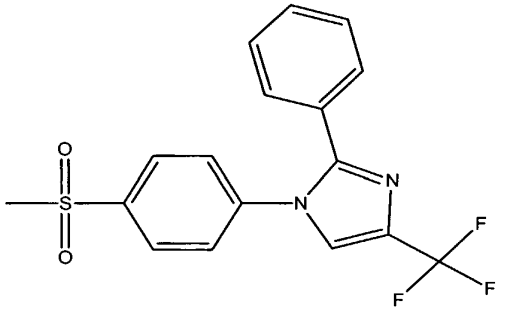
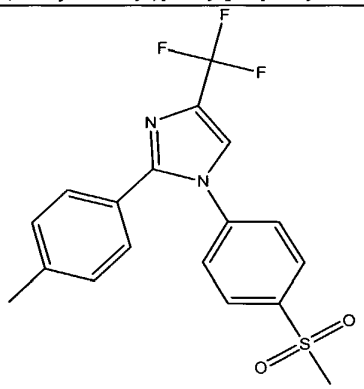
Compound Number	Structural Formula
B-125	 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile;
B-126	 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;
B-127	 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;

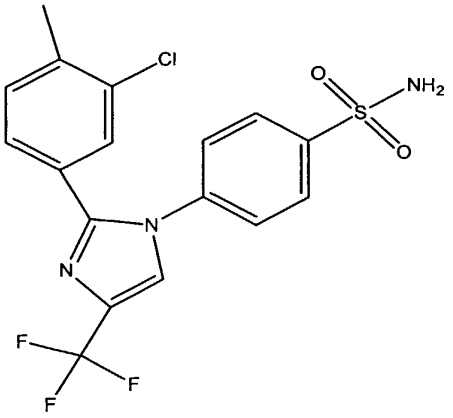
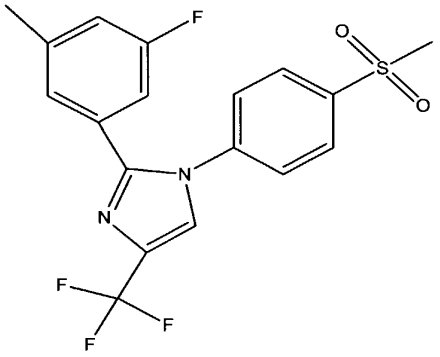
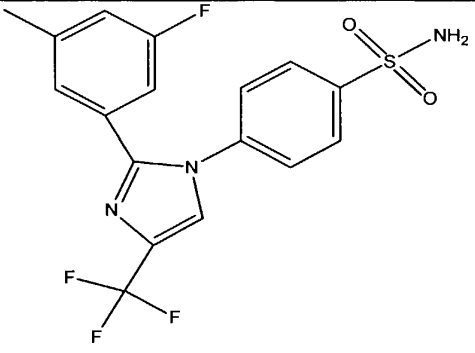
Compound Number	Structural Formula
B-128	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;
B-129	 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;
B-130	 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
B-131	 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine;

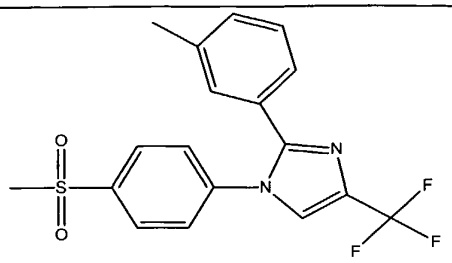
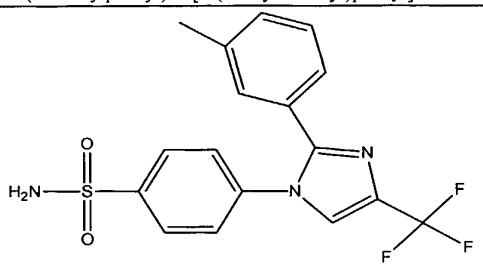
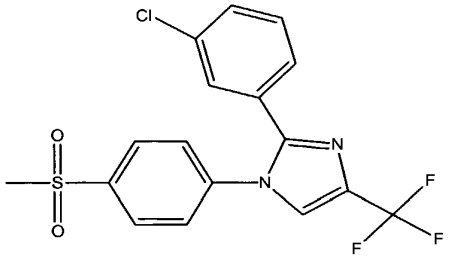
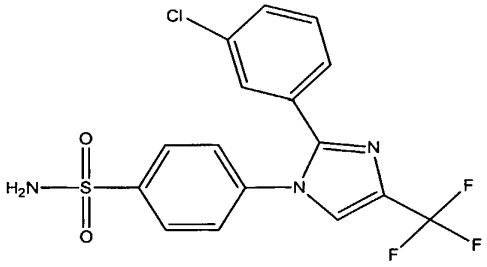
Compound Number	Structural Formula
B-132	 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine;
B-133	 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine;
B-134	 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

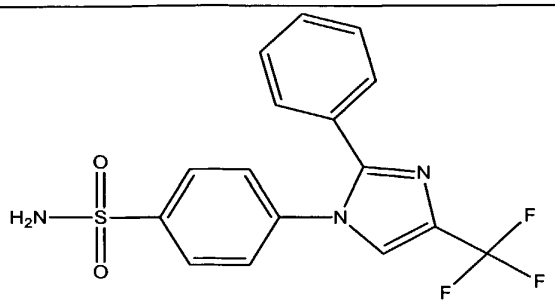
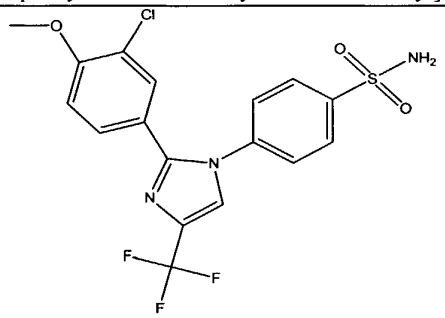
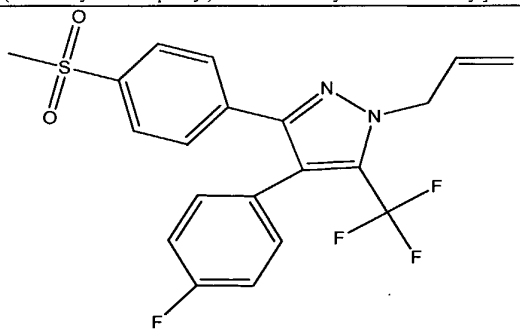
Compound Number	Structural Formula
B-135	 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole;
B-136	 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-137	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

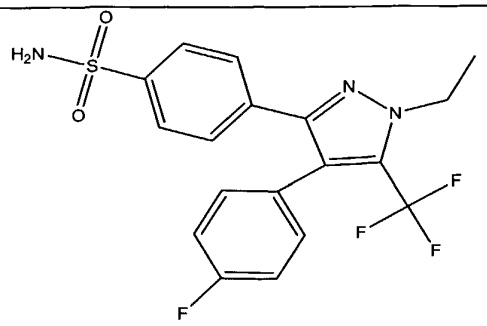
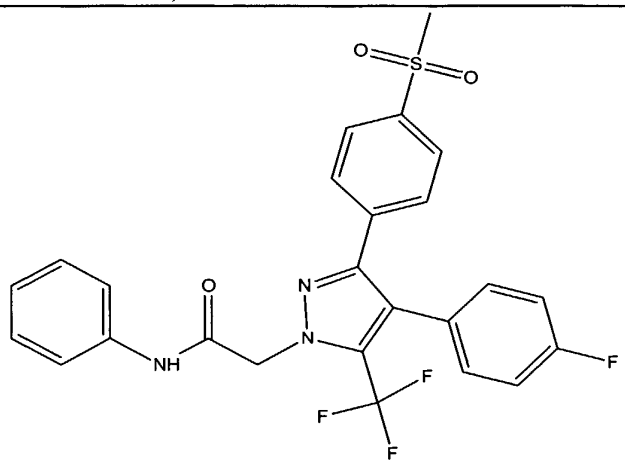
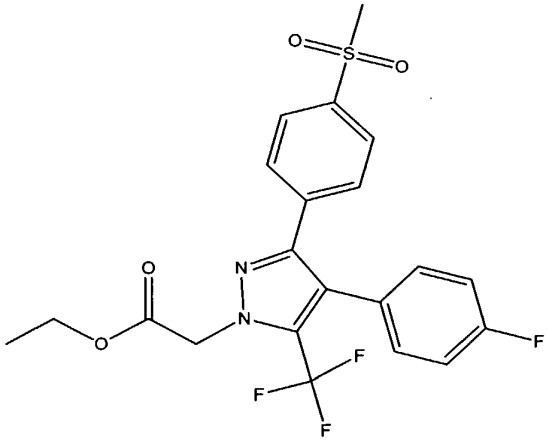
Compound Number	Structural Formula
B-138	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
B-139	 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl] -1H-imidazole;

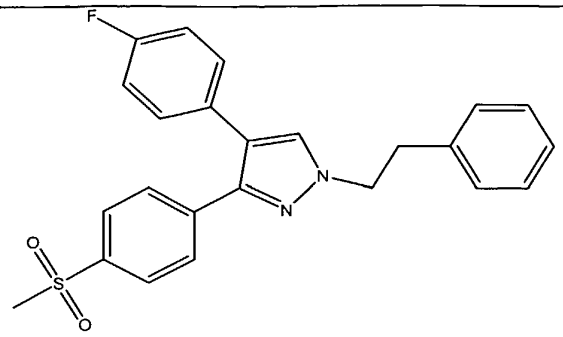
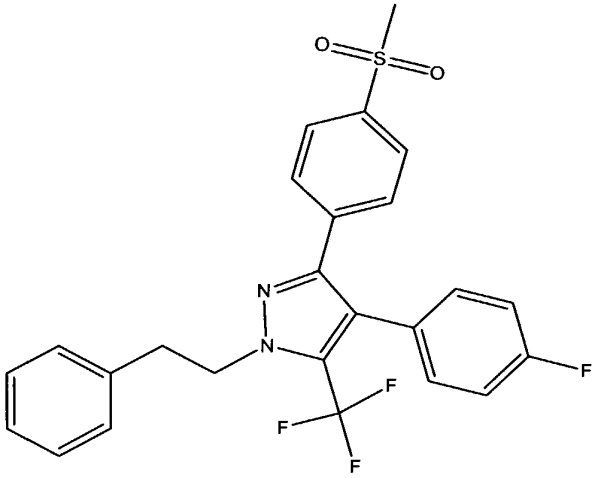
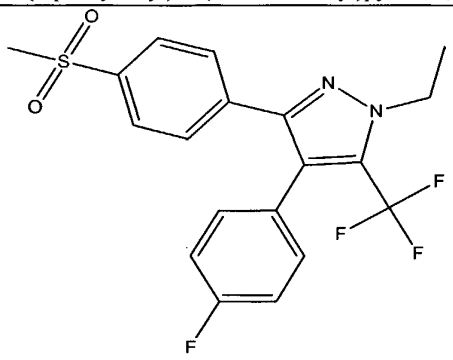
Compound Number	Structural Formula
B-140	 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl -4-(trifluoromethyl)]-1H-imidazole;
B-141	 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
B-142	 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

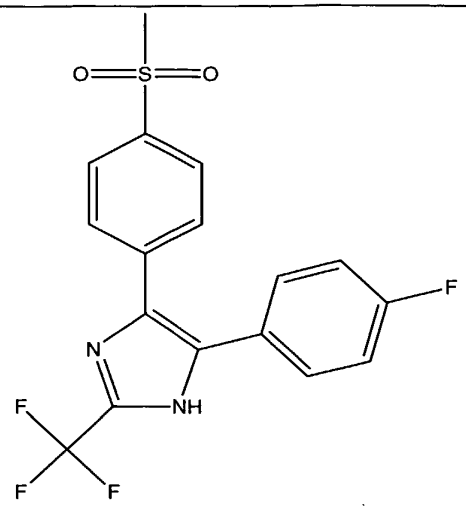
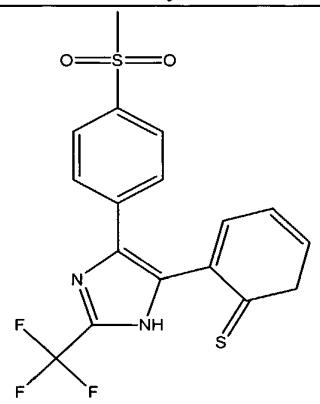
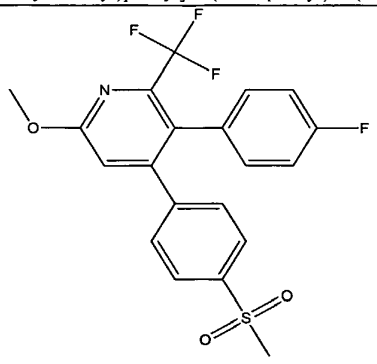
Compound Number	Structural Formula
B-143	 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide;
B-144	 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole;
B-145	 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl -1H-imidazole-1-yl]benzenesulfonamide;

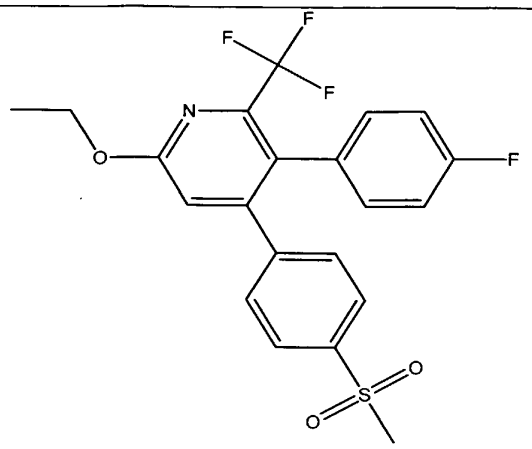
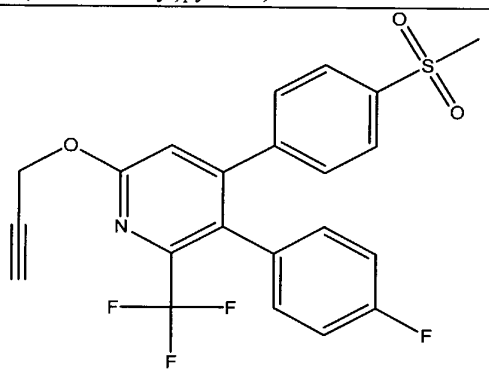
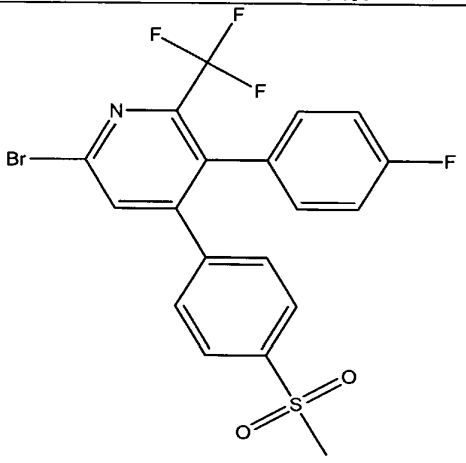
Compound Number	Structural Formula
B-146	 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
B-147	 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-148	 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole
B-149	 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

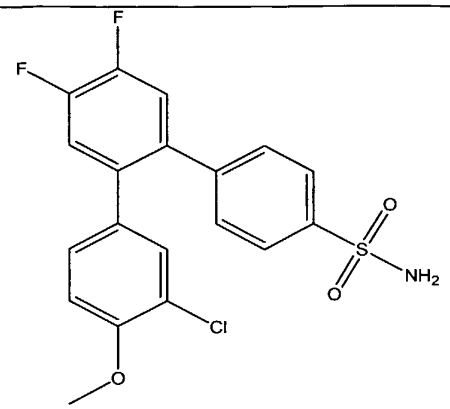
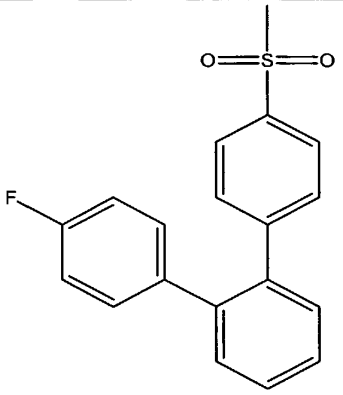
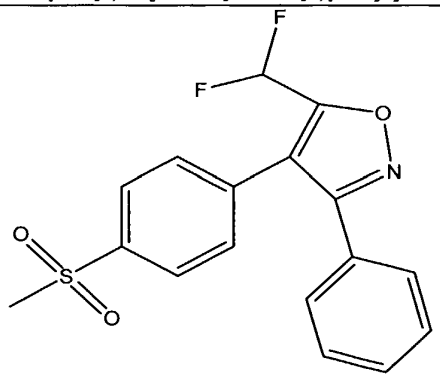
Compound Number	Structural Formula
B-150	 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-151	 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-152	 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole;

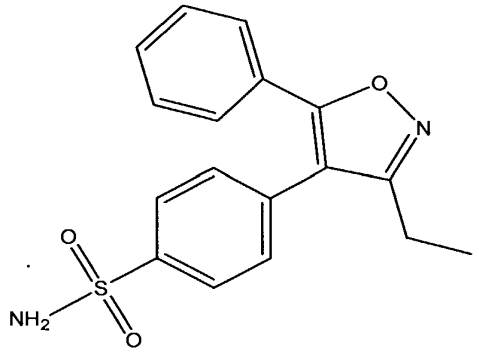
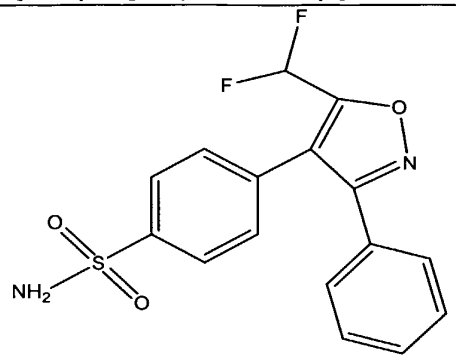
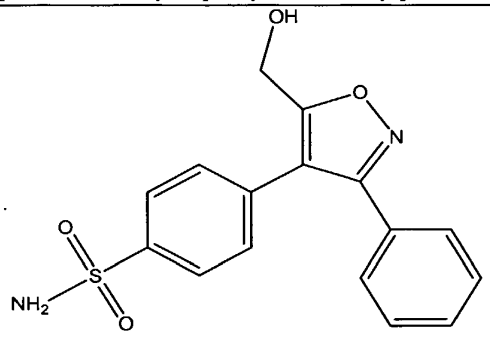
Compound Number	Structural Formula
B-153	 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide;
B-154	 N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
B-155	 ethyl[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

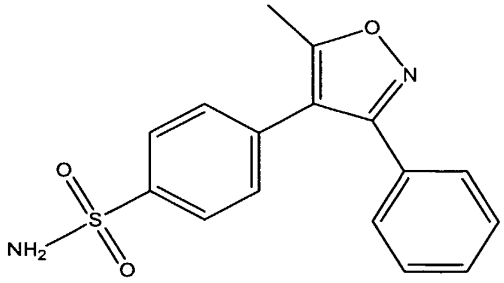
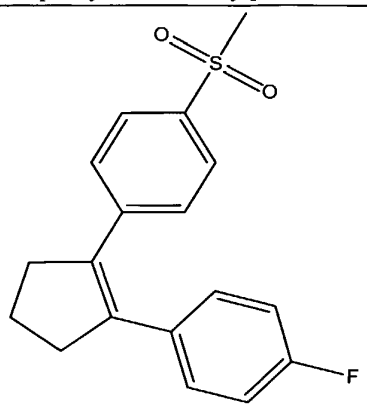
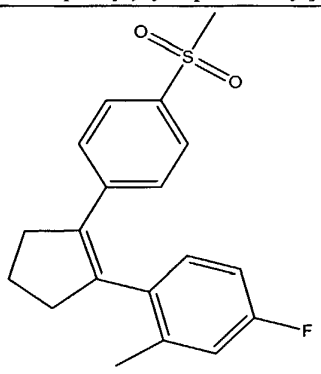
Compound Number	Structural Formula
B-156	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
B-157	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
B-158	 1-ethyl-4-(4-fluorophenyl)-3-[4-methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole;

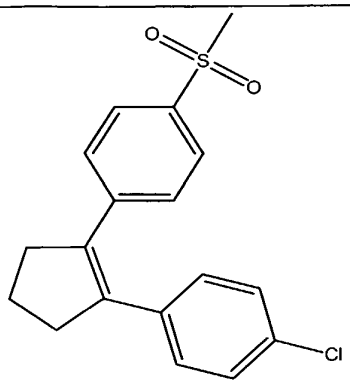
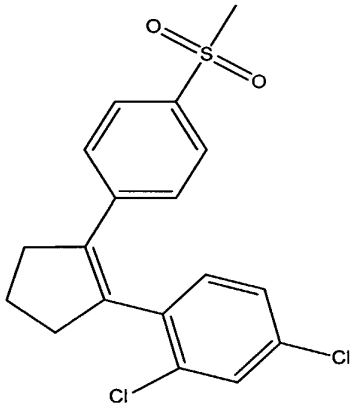
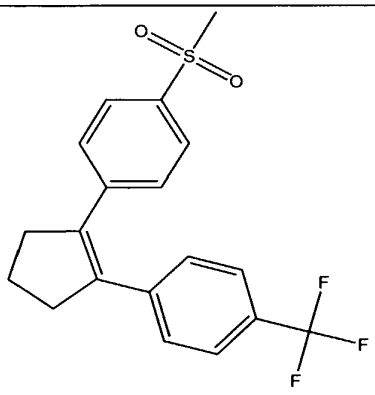
Compound Number	Structural Formula
B-159	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl) -2-trifluoromethyl-1H-imidazole;
B-160	 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
B-161	 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

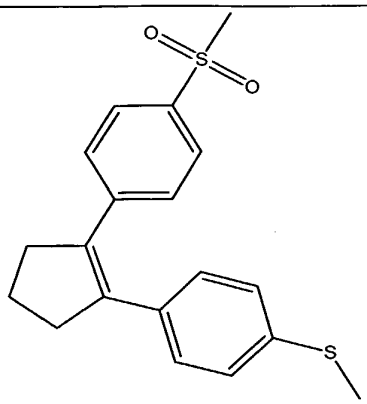
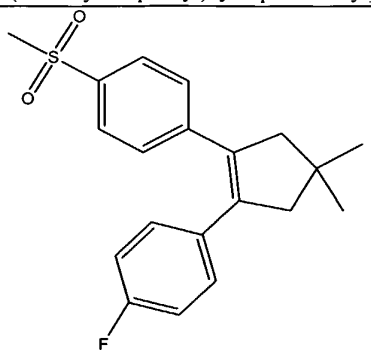
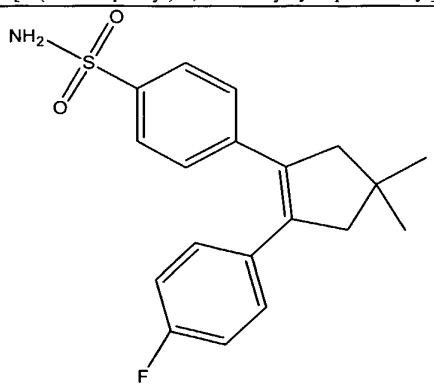
Compound Number	Structural Formula
B-162	 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine;
B-163	 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;
B-164	 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine;

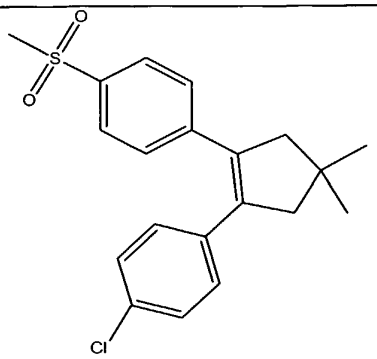
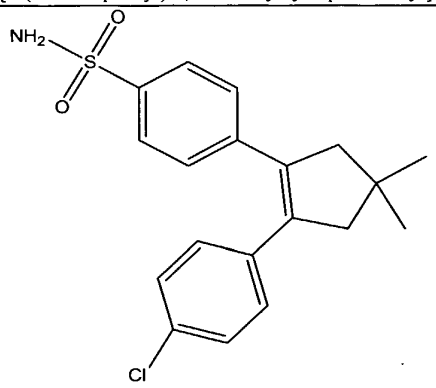
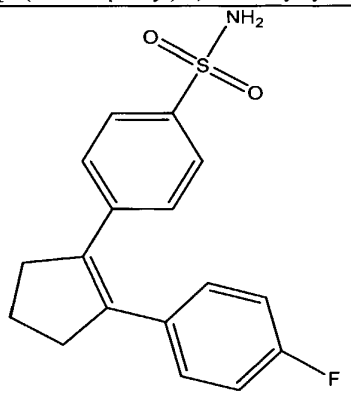
Compound Number	Structural Formula
B-165	 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
B-166	 1-(4-fluorophenyl)-2-[4-methylsulfonyl)phenyl]benzene;
B-167	 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

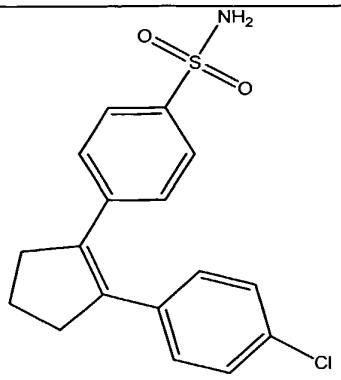
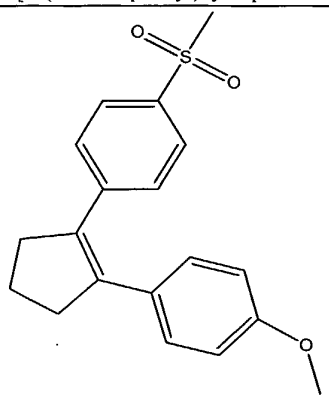
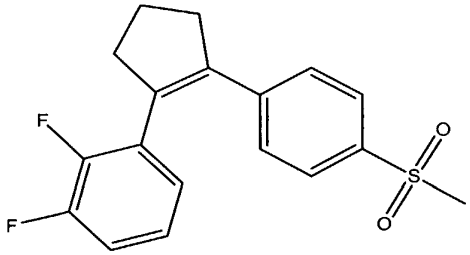
Compound Number	Structural Formula
B-168	 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
B-169	 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-170	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

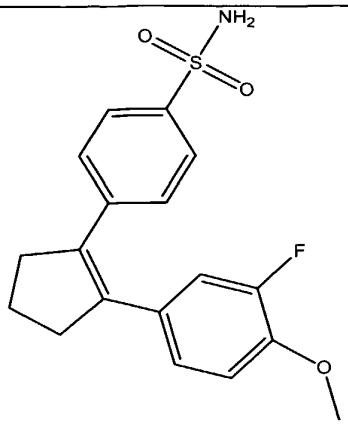
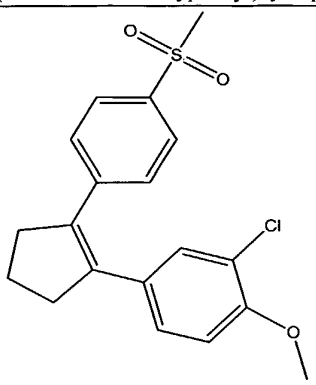
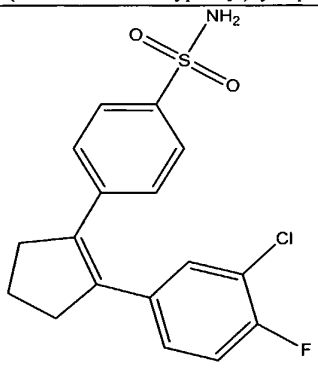
Compound Number	Structural Formula
B-171	 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
B-172	 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-173	 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

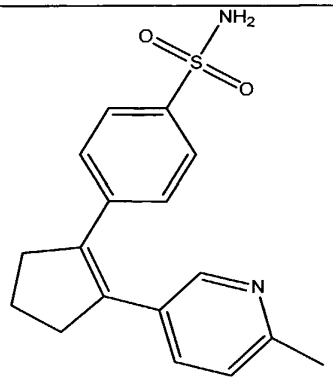
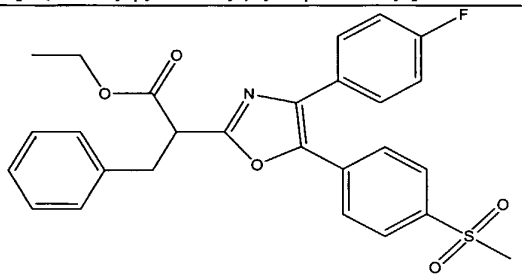
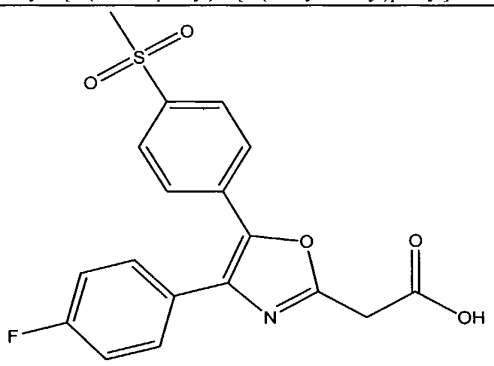
Compound Number	Structural Formula
B-174	 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-175	 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-176	 1-[2-(4-trifloromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

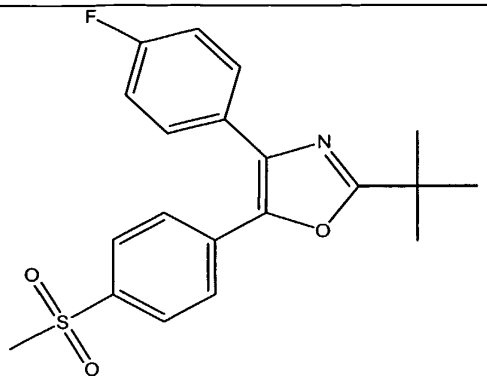
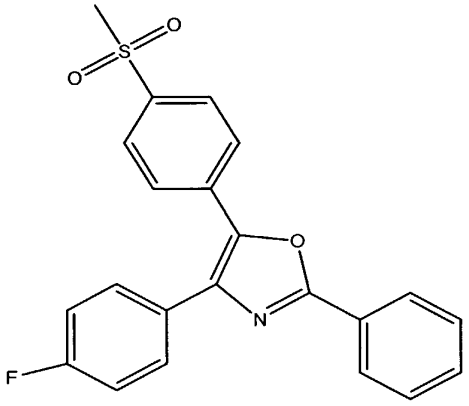
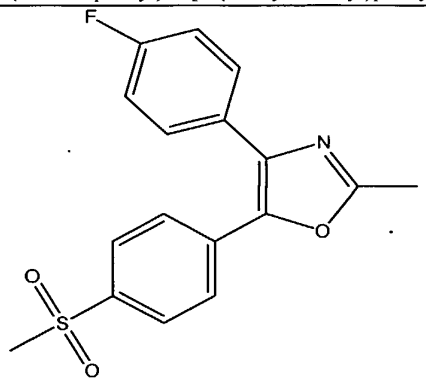
Compound Number	Structural Formula
B-177	 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-178	 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-179	 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

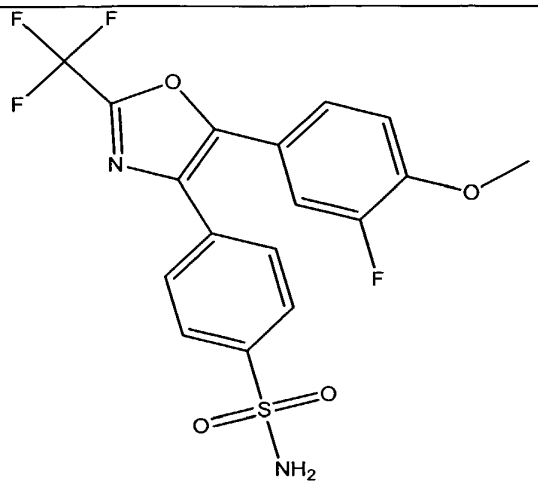
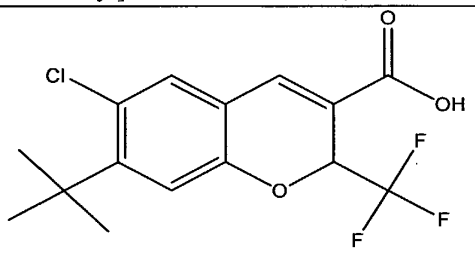
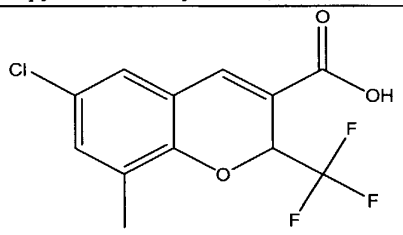
Compound Number	Structural Formula
B-180	 1-[2-(3-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-181	 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
B-182	 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

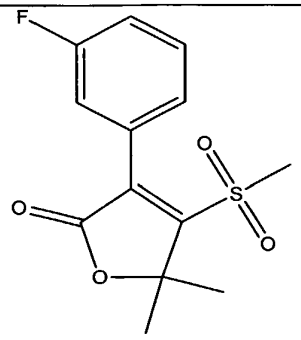
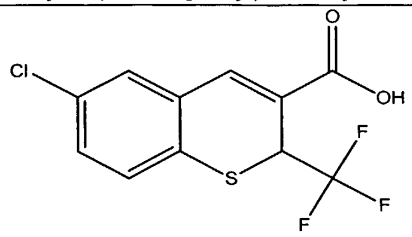
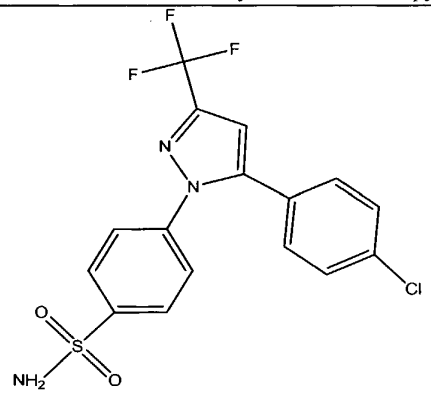
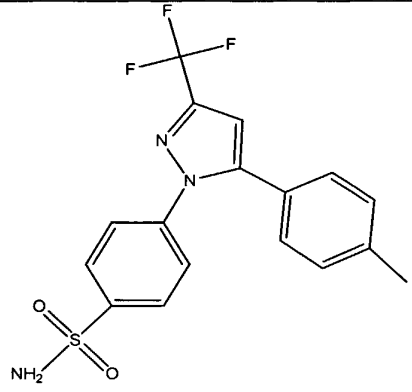
Compound Number	Structural Formula
B-183	 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-184	 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-185	 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

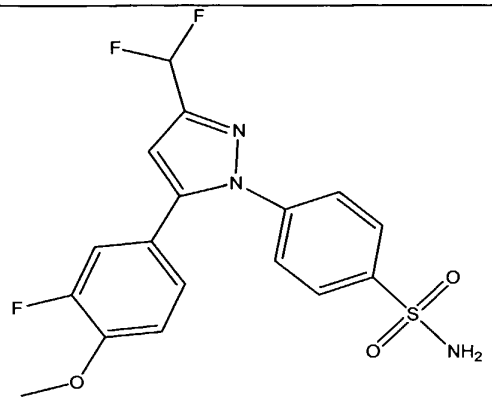
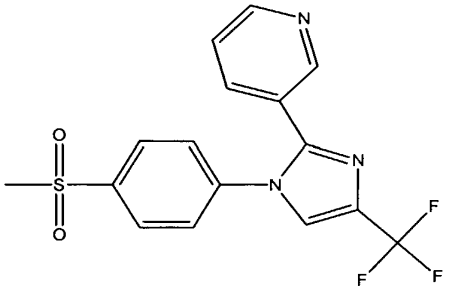
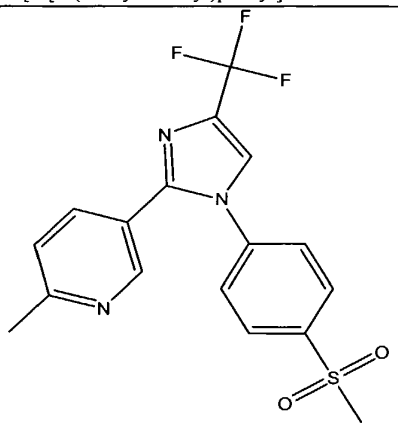
Compound Number	Structural Formula
B-186	 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
B-187	 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-188	 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

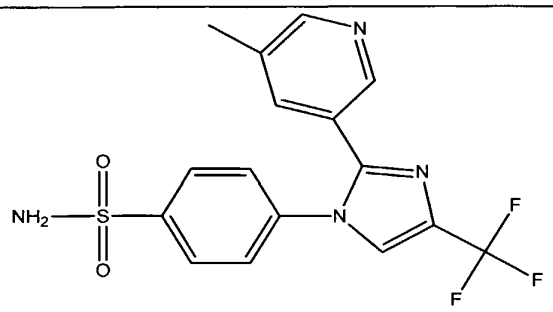
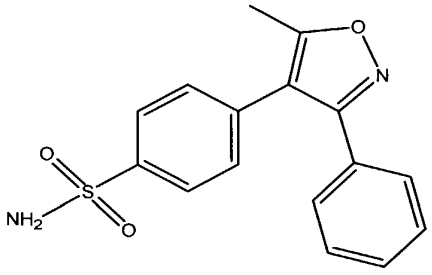
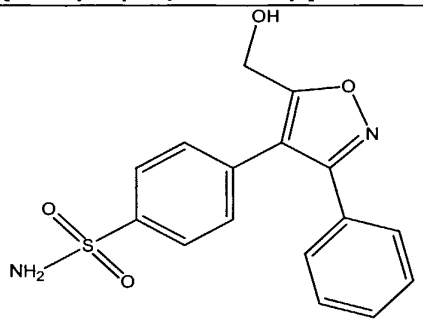
Compound Number	Structural Formula
B-189	 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
B-190	 ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate;
B-191	 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

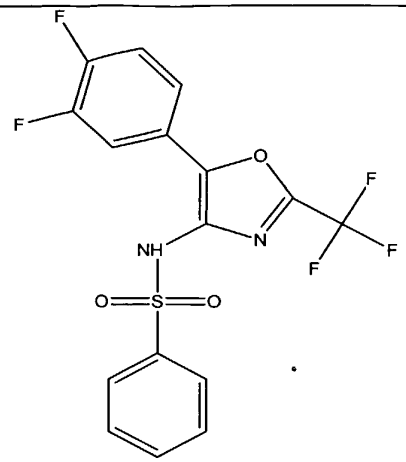
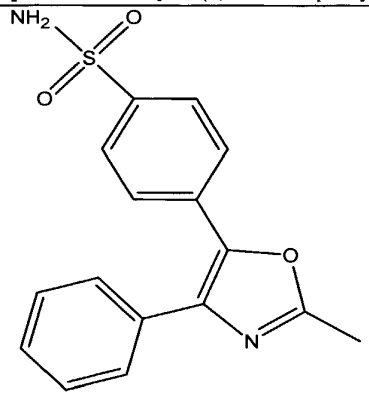
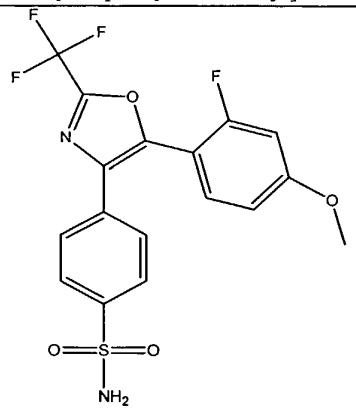
Compound Number	Structural Formula
B-192	 2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
B-193	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;
B-194	 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;

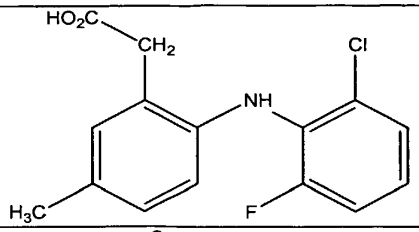
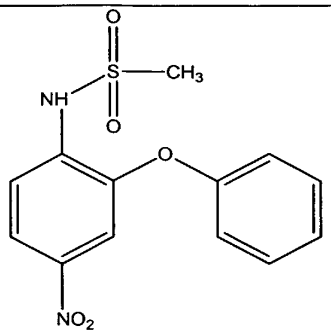
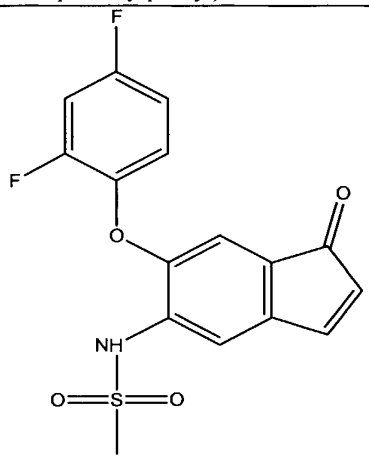
Compound Number	Structural Formula
B-195	 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl -4-oxazolyl]benzenesulfonamide;
B-196	 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H -1-benzopyran-3-carboxylic acid;
B-197	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

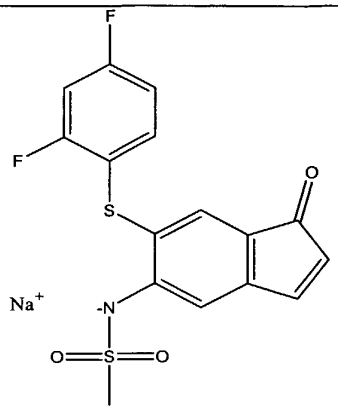
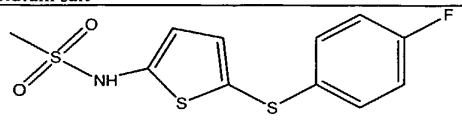
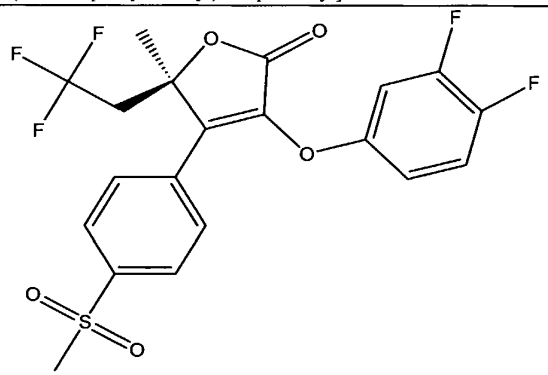
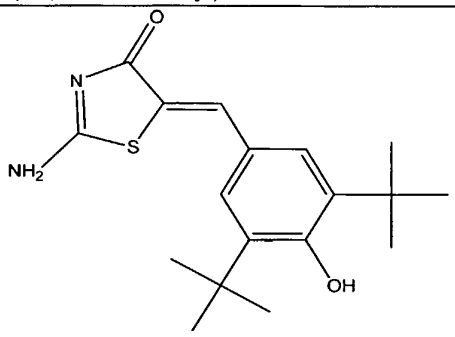
Compound Number	Structural Formula
B-198	 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone;
B-199	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
B-200	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-201	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

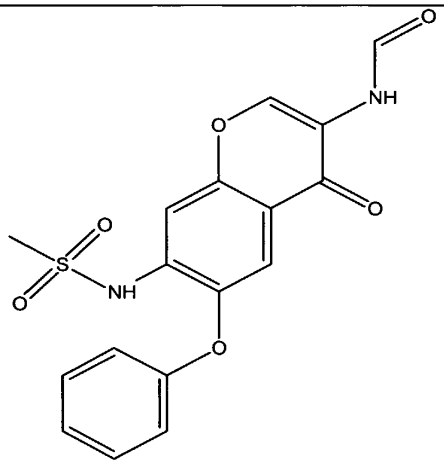
Compound Number	Structural Formula
B-202	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide;
B-203	 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
B-204	 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl -1H-imidazol-2-yl]pyridine;

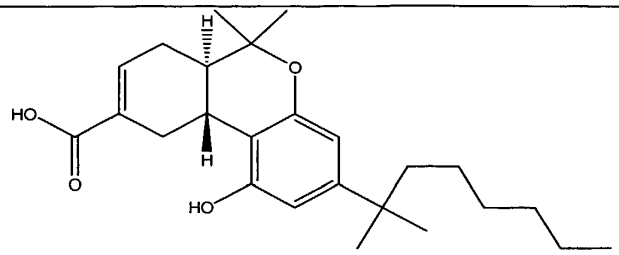
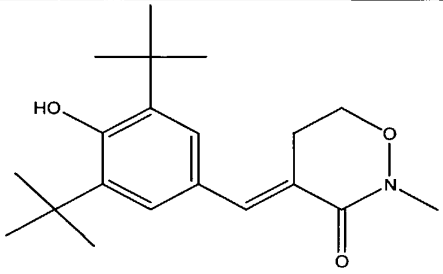
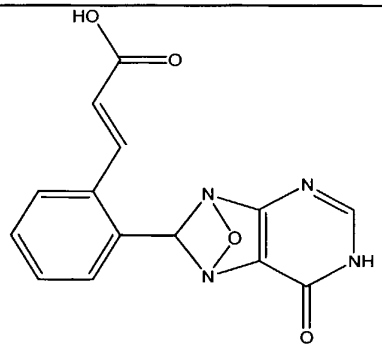
Compound Number	Structural Formula
B-205	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide;
B-206	 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-207	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

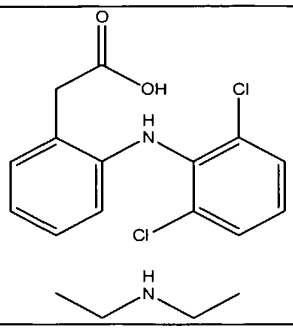
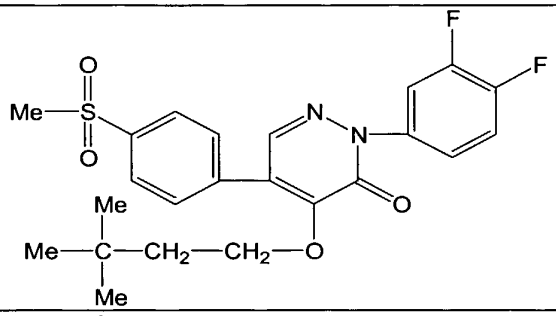
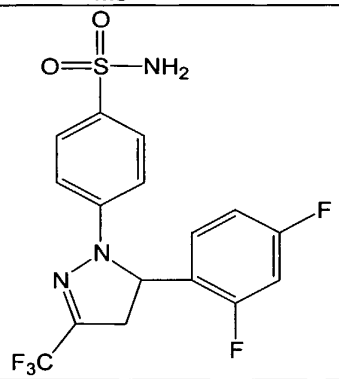
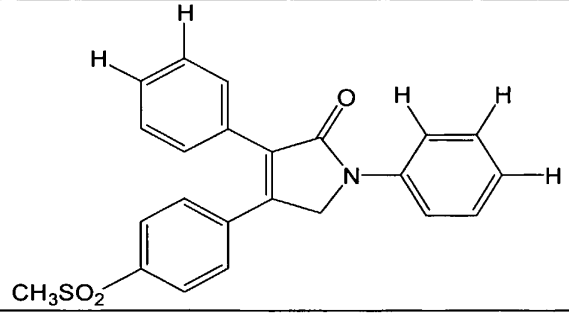
Compound Number	Structural Formula
B-208	 [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
B-209	 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide;
B-210	 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;

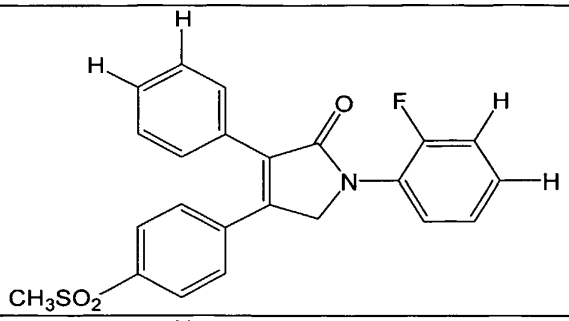
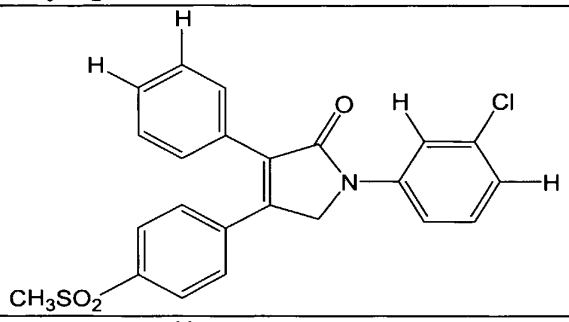
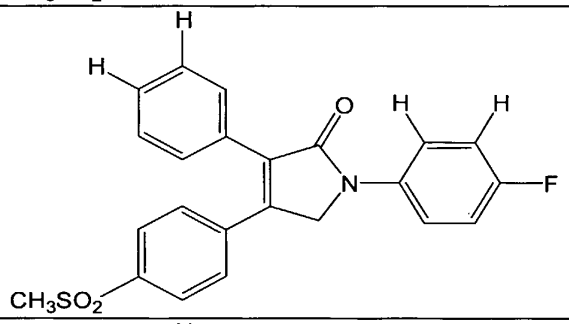
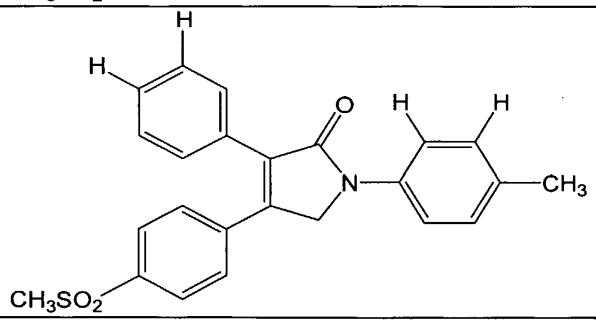
Compound Number	Structural Formula
B-211	
B-212	 *N*-(4-nitro-2-phenoxy-phenyl)-methanesulfonamide
B-213	 N-[6-(2,4-difluoro-phenoxy)-1-oxo-inden-5-yl]-methanesulfonamide

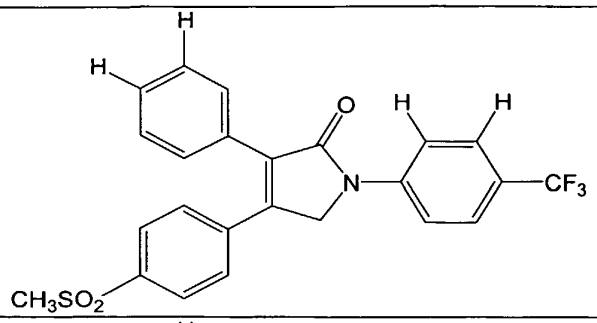
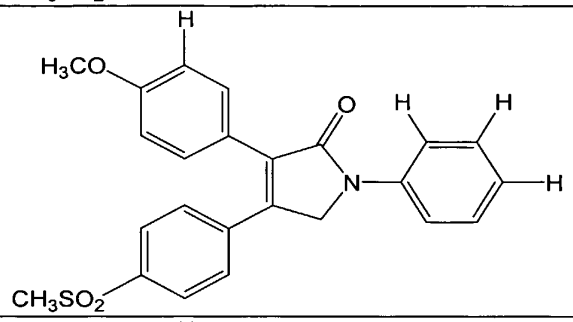
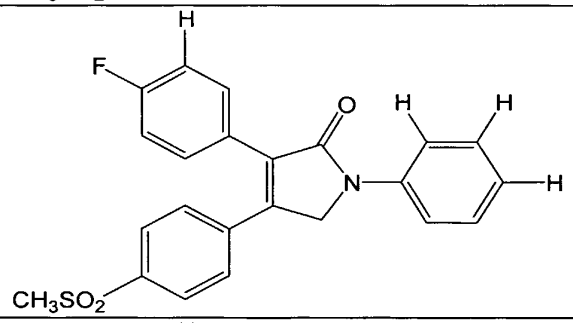
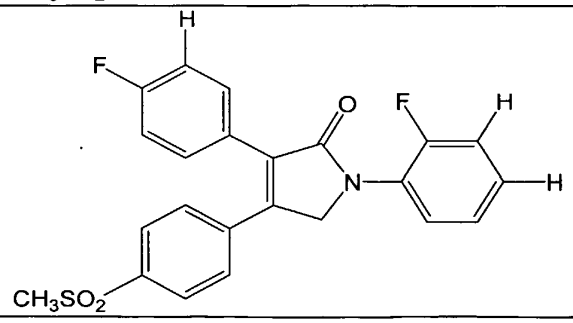
Compound Number	Structural Formula
B-214	 *N*-[6-(2,4-difluoro-phenylsulfanyl)-1-oxo-1*H*-inden-5-yl]-methanesulfonamide, soldium salt
B-215	 N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide
B-216	 3-(3,4-difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl -5-(2,2,2-trifluoro-ethyl)-5*H*-furan-2-one
B-217	 (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] -4(5H)-thiazolone

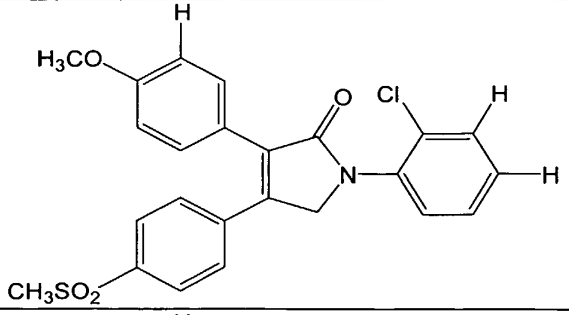
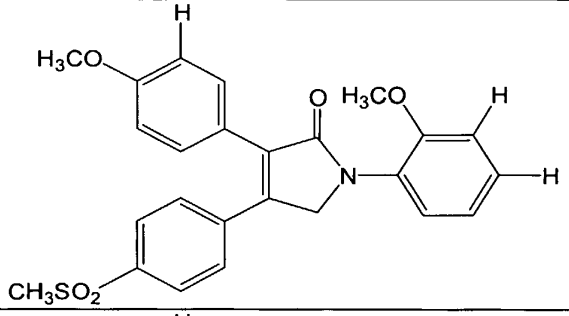
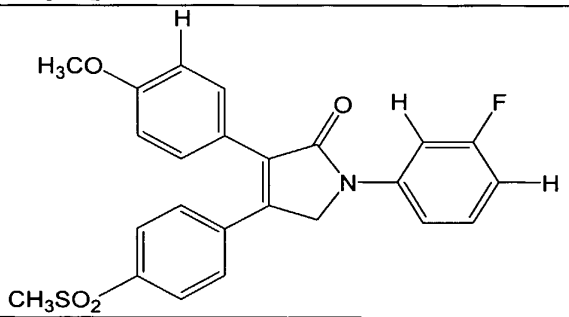
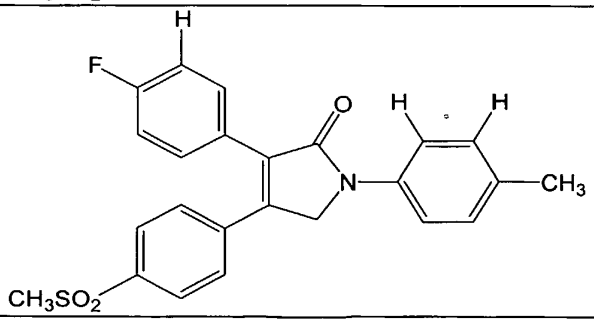
Compound Number	Structural Formula
B-218	CS-502
B-219	LAS-34475
B-220	LAS-34555
B-221	S-33516
B-222	SD-8381
B-223	L-783003
B-224	 N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] -methanesulfonamide
B-225	D-1367
B-226	L-748731

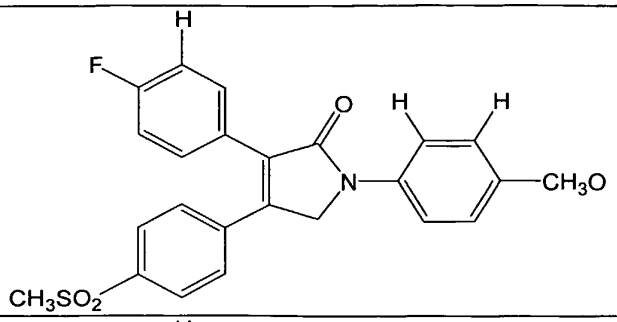
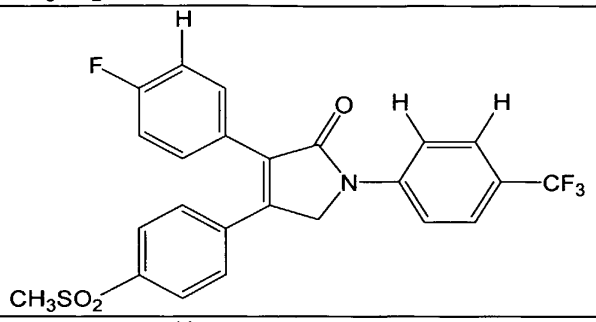
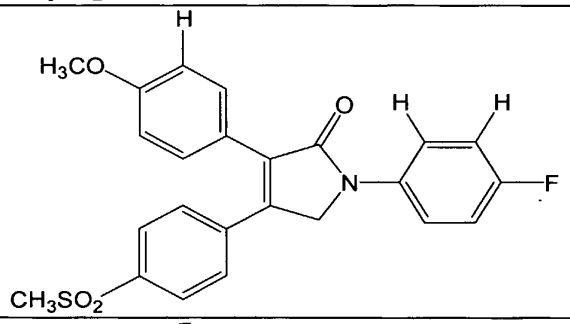
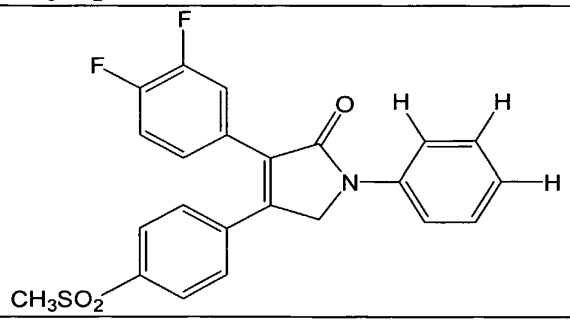
Compound Number	Structural Formula
B-227	 (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid
B-228	CGP-28238
B-229	 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one
B-230	GR-253035
B-231	 2-(6-dioxo-9H-purin-8-yl)cinnamic acid
B-232	S-2474

Compound Number	Structural Formula
B-233	
B-234	
B-235	
B-236	

Compound Number	Structural Formula
B-237	
B-238	
B-239	
B-240	

Compound Number	Structural Formula
B-241	
B-242	
B-243	
B-244	

Compound Number	Structural Formula
B-245	
B-246	
B-247	
B-248	

Compound Number	Structural Formula
B-249	
B-250	
B-251	
B-252	

[0415] The cyclooxygenase-2 selective inhibitor employed in the present invention can exist in tautomeric, geometric or stereoisomeric forms. Generally speaking, suitable cyclooxygenase-2 selective inhibitors that are in tautomeric, geometric or stereoisomeric forms are those compounds that inhibit cyclooxygenase-2 activity by about 25%, more typically by about 50%, and even more typically, by about

75% or more when present at a concentration of 100 μM or less. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof. Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric forms are also included within the invention. The terms "cis" and "trans", as used herein, denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans"). Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms. Furthermore, some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures or R and S forms for each stereocenter present.

[0416] The cyclooxygenase-2 selective inhibitors utilized in the present invention may be in the form of free bases or pharmaceutically acceptable acid addition salts thereof. The term "pharmaceutically-acceptable salts" are salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt may vary, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds for use in the present methods may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of use in the present methods include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for

example, the appropriate acid or base with the compound of any Formula set forth herein.

[0417] The cyclooxygenase-2 selective inhibitors of the present invention can be formulated into pharmaceutical compositions and administered by a number of different means that will deliver a therapeutically effective dose. Such compositions can be administered orally, parenterally, by inhalation spray, rectally, intradermally, transdermally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania (1975), and Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y. (1980).

[0418] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

[0419] Suppositories for rectal administration of the compounds discussed herein can be prepared by mixing the active agent with a suitable non-irritating excipient such as cocoa butter, synthetic mono-, di-, or triglycerides, fatty acids, or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature, and which will therefore melt in the rectum and release the drug.

[0420] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds are

ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

[0421] For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

[0422] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[0423] The amount of active ingredient that can be combined with the carrier materials to produce a single dosage of the cyclooxygenase-2 selective inhibitor will vary depending upon the patient and the particular mode of administration. In general, the pharmaceutical compositions may contain a cyclooxygenase-2 selective inhibitor in the range of about 0.1 to 2000 mg, more typically, in the range of about 0.5 to 500 mg and still more typically, between about 1 and 200 mg. A daily dose of about 0.01 to 100 mg/kg body weight, or more typically, between about 0.1 and about 50 mg/kg body weight and even more typically, from about 1 to 20 mg/kg body weight, may be

appropriate. The daily dose is generally administered in one to about four doses per day.

[0424] In one embodiment, when the cyclooxygenase-2 selective inhibitor comprises rofecoxib, it is typical that the amount used is within a range of from about 0.15 to about 1.0 mg/day·kg, and even more typically, from about 0.18 to about 0.4 mg/day·kg.

[0425] In still another embodiment, when the cyclooxygenase-2 selective inhibitor comprises etoricoxib, it is typical that the amount used is within a range of from about 0.5 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0426] Further, when the cyclooxygenase-2 selective inhibitor comprises celecoxib, it is typical that the amount used is within a range of from about 1 to about 20 mg/day·kg, even more typically, from about 1.4 to about 8.6 mg/day·kg, and yet more typically, from about 2 to about 3 mg/day·kg.

[0427] When the cyclooxygenase-2 selective inhibitor comprises valdecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0428] In a further embodiment, when the cyclooxygenase-2 selective inhibitor comprises parecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 1 to about 3 mg/day·kg.

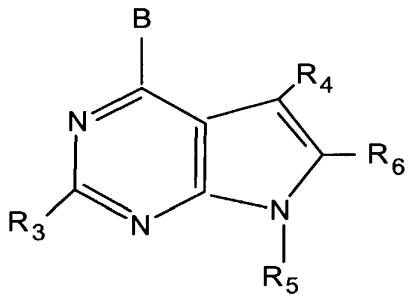
[0429] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

CORTICOTROPIN RELEASING FACTOR ANTAGONISTS

[0430] In addition to a cyclooxygenase-2 selective inhibitor, the combination therapy of the present invention comprises a corticotropin releasing factor antagonist. In one embodiment, the corticotropin releasing factor antagonist in this therapeutic combination is selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695 (N-(2-chloro-4,6-dimethylphenyl)-1-[1-methoxymethyl-(2-

methoxyethyl]-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine mesylate)), D-PheCRF 12-41, and N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine. In one embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41, antalarmin, CP-154,526, and astressin. In another embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41 and antalarmin. In yet another embodiment, the corticotropin releasing factor antagonist of this therapeutic combination is α-helical CRF 9-41.

[0431] In one embodiment, the corticotropin releasing factor antagonist is represented by Formula *(VI)*:



(VI)

[0432] wherein:

[0433] B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCR_1R_2R_{11}$, $-OCR_1R_2R_{11}$, $-SCR_1R2R_{11}$, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$, $-CR_2R_{11}OR_1$, $-CR_2R_{11}SR_1$, or $-C(O)R_2$;

[0434] R_1 is hydrogen, or C_1-C_6 alkyl optionally substituted with from one to two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, $-O(C_1$-C_6 alkyl), $-ONH(C_1$-C_4 alkyl), $-ON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), amino, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl), $-S(C_1$-C_6 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-NH(C_1$-C_4 alkyl), -COOH, $-O(C_1$-C_4 alkyl), $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2$ (C_1-C_4 alkyl), $-SO_2$ NH(C_1-C_4 alkyl), $-SO_2$ (C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein each of the foregoing C_1-C_6 alkyl moieties in the definition of R_1 may contain one or two double or triple bonds;

[0435] R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl,

furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein one or two of the carbon atoms of any of said cycloalkyl moieties may optionally be replaced, independently, by O, S or -N-Z wherein Z is hydrogen, C_1-C_4 alkyl or C_1-C_4 alkanoyl, and wherein R_2 may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or by one substituent selected from hydroxy, bromo, iodo, C_1-C_6 alkoxy, -O(C_1-C_6 alkyl), -ON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl) (C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -COOH, -O(C_1-C_4 alkyl), -NH(C1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2 (C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein each of the foregoing C_1-C_{12} alkyl and C_1-C_{10} alkylene moieties in the definition may optionally contain one to three double or triple bonds; or R_1 and R_2, taken together with the atom to which they are attached, may form a saturated 3- to 8-membered ring which, if it is a 5- to 8-membered ring, may optionally contain one to two double bonds, and wherein one or two of the carbon atoms of said 5- to 8- membered ring may optionally be replaced, independently, by O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl or benzyl;

[0436] R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), or -SO_2 (C_1-C_4 alkyl), wherein each of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the definition of R_3 may contain one double or triple bond and may optionally be substituted with from 1 to 3 substituents independently selected from the group consisting of hydroxy, C_1-C_3 alkoxy, fluoro, chloro or C_1-C_3 thioalkyl;

[0437] R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_2 alkyl), -SO_n (C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein each of the foregoing C_1-C_6 alkyl moieties in the definition of R_4 may optionally be substituted with one substituent selected from hydroxy, trifluoromethyl, amino, carboxy, amido, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano and nitro;

[0438] R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl,

benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolindinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or a 3- or 8-membered cycloalkyl or 9- or 12-membered bicycloalkyl ring, wherein one or two of the carbon atoms in said ring may optionally be replaced, independently, by O, S or -N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, and wherein each of the above R_5 groups may optionally be substituted with one or more substituents, preferably with two or three substituents, independently selected from fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and trifluoromethyl, or with one substituent selected from hydroxy, iodo, cyano, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -S(C_1-C_6 alkyl), -SO_2(C_1-C_6 alkyl), and wherein each of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the definition of R_5 may optionally be substituted with from one to two substituents independently selected from fluoro, chloro, hydroxy, C_1-C_4 alkoxy, amino, methylamino, dimethylamino and acetyl, and wherein each of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the definition of R_5 may optionally contain one double or triple bond; with the proviso that R_5 is not unsubstituted phenyl;

[0439] R_6 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_2 alkyl), -SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, and wherein each of the foregoing (C_1-C_6)alkyl moieties in the definition of R_6 may be optionally substituted with one substituent selected from hydroxy, trifluoromethyl, amino, carboxy, amido, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano and nitro;

[0440] R_7 is hydrogen, hydroxy, fluoro, chloro, -COO(C_1-C_2 alkyl), cyano, or -CO(C_1-C_2 alkyl); and

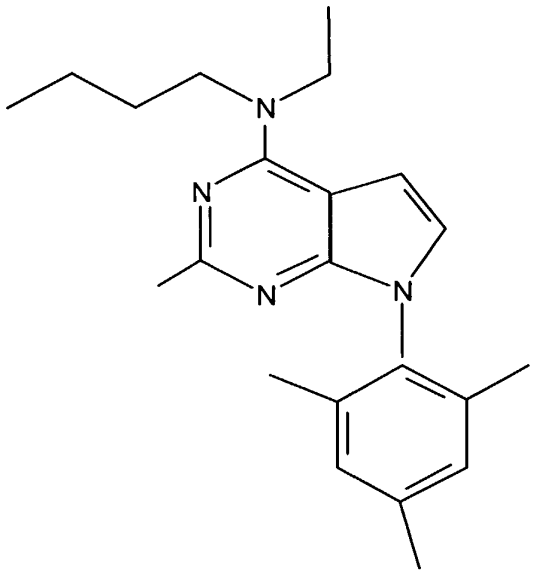
[0441] R_8 is hydrogen or C_1-C_4 alkyl;

[0442] with the proviso that:

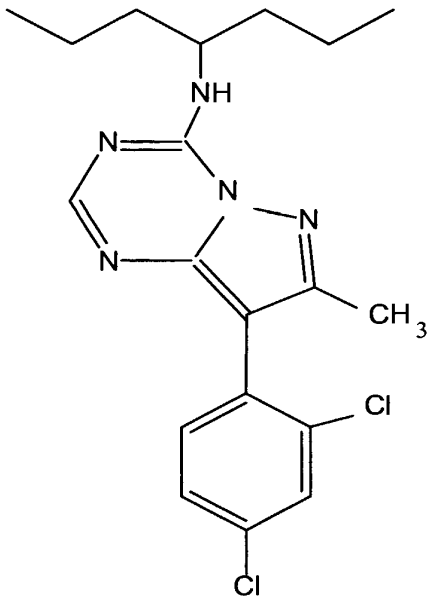
[0443] B is not a straight chain alkyl when R_5 is unsubstituted cycloalkyl, R_3 and R_4 are both hydrogen and R_6 is hydrogen or methyl; B is not NHR_2 wherein R_2 is benzyl or thienylmethyl; and B is not methylamino or hydroxyethylamino when R_5 is p-bromophenyl and R_3, R_4 and R_6 are methyl.

[0444] Suitable examples of compounds having formula VI are described in WO 94/13676, which is hereby incorporated by reference in its entirety.

[0445] In another embodiment, the corticotropin releasing factor antagonist is CP-154,526, having the formula:



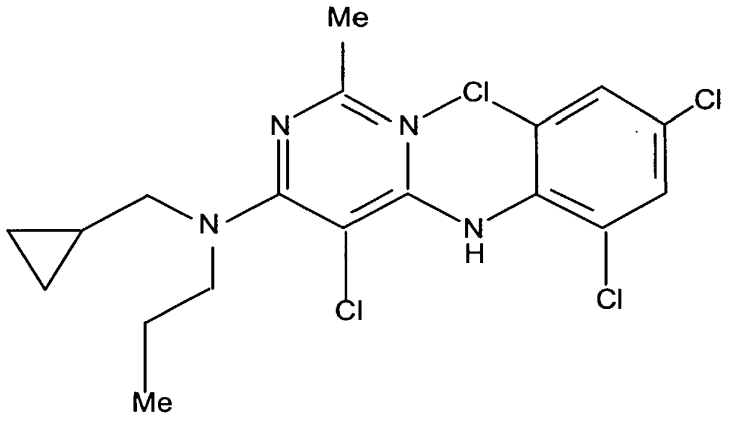
[0446] In yet another embodiment of the invention, the corticotropin releasing factor antagonist is DMP 696, having the formula:



[0447] In still another embodiment of the invention, the corticotropin releasing factor antagonist is α-helical CRF 9-41, having the sequence:

[0448] Asp-Leu-Thr-Phe-His-Leu-Arg-Glu-Met-Leu-Glu-Met-Ala-Lys-ala-Glu-Gln-Ala-Glu-Gln-Ala-Leu-Asn-Arg-Leu-Leu-Glu-Ala-NH2 (Sequence ID No.1).

[0449] In another embodiment of the invention, the corticotropin releasing factor antagonist is NBI 27914 hydrochloride, having the formula:



[0450] Generally speaking, the corticotropin releasing antagonist can be administered as a pharmaceutical composition with or without a carrier. The terms "pharmaceutically acceptable carrier" or "carrier" refer to any generally acceptable excipient or drug delivery composition that is relatively inert and non-toxic. Exemplary carriers include sterile water, salt solutions (such as Ringer's solution), alcohols, gelatin, talc, viscous paraffin, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, calcium carbonate, carbohydrates (such as lactose, sucrose, dextrose, mannose, albumin, starch), cellulose, silica gel, polyethylene glycol (PEG), dried skim milk, rice flour, magnesium stearate, and the like. Suitable formulations and additional carriers are described in Remington's Pharmaceutical Sciences, (17.sup.th Ed., Mack Pub. Co., Easton, Pa.). Such preparations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, preservatives and/or aromatic substances and the like which do not deleteriously react with the active compounds. Typical preservatives can include, potassium sorbate, sodium metabisulfite, methyl paraben, propyl paraben, thimerosal, etc. The compositions can also be combined

where desired with other active substances, e.g., enzyme inhibitors, to reduce metabolic degradation.

[0451] Moreover, the corticotropin releasing antagonist can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The method of administration can dictate how the composition will be formulated. For example, the composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, or magnesium carbonate.

[0452] In another embodiment, the corticotropin releasing antagonist can be administered intravenously, parenterally, intramuscularly, subcutaneously, orally, nasally, topically, by inhalation, by implant, by injection, or by suppository. For enteral or mucosal application (including via oral and nasal mucosa), particularly suitable are tablets, liquids, drops, suppositories or capsules. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Liposomes, microspheres, and microcapsules are available and can be used. Pulmonary administration can be accomplished, for example, using any of various delivery devices known in the art such as an inhaler. See. e.g. S. P. Newman (1984) in Aerosols and the Lung, Clarke and Davis (eds.), Butterworths, London, England, pp. 197-224; PCT Publication No. WO 92/16192; PCT Publication No. WO 91/08760. For parenteral application, particularly suitable are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-polyoxypropylene block polymers, and the like.

[0453] The actual effective amounts of compound or drug can and will vary according to the specific composition being utilized, the mode of administration and the age, weight and condition of the subject. Dosages for a particular individual subject can be determined by one of ordinary skill in the art using conventional considerations.

[0454] By way of example, in one embodiment when the corticotropin releasing antagonist is α-helical CRF 9-41, the amount administered daily is typically from about 0.5 to about 3500 milligrams. In an alternative of this embodiment, the amount of α-helical CRF 9-41 administered daily is between about 1 and about 50 milligrams/kilogram of the subject's weight. In another alternative of this embodiment,

the amount of α-helical CRF 9-41 administered daily is between about 5 and about 20 milligrams/kilogram of the subject's weight.

[0455] By way of further example, in another embodiment the corticotropin releasing antagonist is antalarmin, and the amount administered daily is typically from about 50 to about 4000 miligrams. In an alternative of this embodiment, the amount of antalarmin administered daily is between about 1 and 50 milligrams/kilogram of the subject's weight. In another alternative of this embodiment, the amount of antalarmin administered daily is between about 5 and about 30 milligrams/kilogram of the subject's weight.

[0456] Moreover, the corticotropin releasing factor antagonist can be a combination of two or more different corticotropin releasing antagonists. The multiple antagonists can be administered separately or may be co-administered as a single composition and may be administered as discussed above.

[0457] By way of example, in another embodiment the corticotropin releasing antagonist is a combination of α-helical CRF 9-41 and antalarmin, and the amount of the combination antagonist administered daily is typically from about 0.1 to about 1000 μg. In an alternative of this embodiment, the amount of the combination antagonist administered daily is between about 1 and 50 milligrams/ kilogram of the subject's weight. In another alternative of this embodiment, the amount of the combination antagonist administered daily is between about 5 and about 25 milligrams/ kilogram of the subject's weight.

[0458] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

[0459] Generally speaking, when the composition is administered to treat an ischemic mediated condition, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered to the subject as soon as possible after the reduction in blood flow to the central nervous system in order to reduce the extent of ischemic damage. Typically, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered within about 10 days after the reduction of blood flow to the central nervous system and more typically, within 24 hours. In still another embodiment, the corticotropin releasing factor antagonist and

cyclooxygenase-2 selective inhibitor are administered from about 1 to about 12 hours after the reduction in blood flow to the central nervous system. In another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 6 hours after the reduction in blood flow to the central nervous system. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 3 to about 4 hours after the reduction in blood flow to the central nervous system. In yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 2 hours after the reduction in blood flow to the central nervous system.

[0460] Generally speaking, when the composition is administered to prevent an ischemic mediated condition, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered to the subject such that the antagonist has sufficient time to bind to the corticotropin releasing factor receptors and/or to exact its preventative effects. Typically, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered within about 24 hours before the reduction of blood flow to the central nervous system and more typically, within about 12 hours. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered from about 1 to about 12 hours before the reduction in blood flow to the central nervous system. In another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 6 hours before the reduction in blood flow to the central nervous system. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 3 to about 4 hours before the reduction in blood flow to the central nervous system. In yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 2 hours before the reduction in blood flow to the central nervous system. In still a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 1 hour before the reduction in blood flow to the central nervous system. In still yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 1/2 hour before the reduction in blood flow to the central nervous system.

[0461] Moreover, the timing of the administration of the cyclooxygenase-2 selective inhibitor in relation to the administration of the corticotropin releasing factor antagonist may also vary from subject to subject. In one embodiment, the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist may be administered substantially simultaneously, meaning that each agent may be administered to the subject at approximately the same time. For example, the cyclooxygenase-2 selective inhibitor is administered during a continuous period beginning on the same day as the beginning of the corticotropin releasing factor antagonist and extending to a period after the end of the corticotropin releasing factor antagonist. Alternatively, the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist may be administered sequentially, meaning that they are each administered at separate times during separate treatments. In one embodiment, for example, the cyclooxygenase-2 selective inhibitor is administered during a continuous period beginning prior to administration of the corticotropin releasing factor antagonist and ending after administration of the corticotropin releasing factor antagonist. Of course, it is also possible that the cyclooxygenase-2 selective inhibitor may be administered either more or less frequently than the corticotropin releasing factor antagonist. Moreover, it will be apparent to those skilled in the art that it is possible, and perhaps desirable, to combine various times and methods of administration in the practice of the present invention.

COMBINATION THERAPIES

[0462] Generally speaking, it is contemplated that the composition employed in the practice of the invention may include one or more of any of the cyclooxygenase-2 selective inhibitors detailed above in combination with one or more of any of the corticotropin releasing factor antagonists detailed above. By way of a non-limiting example, Table 4a details a number of suitable combinations that are useful in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4a.

TABLE 4a

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing Factor Antagonist
a compound having formula I	α-helical CRF 9-41
a compound having formula I	antalarmin
a compound having formula I	astressin
a compound having formula I	NBI 27914
a compound having formula I	R121919
a compound having formula I	R121920
a compound having formula I	antisauvagine-30
a compound having formula I	DMP-695
a compound having formula I	CP-154,526
a compound having formula II	α-helical CRF 9-41
a compound having formula II	antalarmin
a compound having formula II	astressin
a compound having formula II	NBI 27914
a compound having formula II	R121919
a compound having formula II	R121920
a compound having formula II	antisauvagine-30
a compound having formula II	DMP-695
a compound having formula II	CP-154,526
a compound having formula III	α-helical CRF 9-41
a compound having formula III	antalarmin
a compound having formula III	astressin
a compound having formula III	NBI 27914
a compound having formula III	R121919
a compound having formula III	R121920
a compound having formula III	antisauvagine-30
a compound having formula III	DMP-695
a compound having formula III	CP-154,526
a compound having formula IV	α-helical CRF 9-41
a compound having formula IV	antalarmin
a compound having formula IV	astressin
a compound having formula IV	NBI 27914
a compound having formula IV	R121919
a compound having formula IV	R121920
a compound having formula IV	antisauvagine-30
a compound having formula IV	DMP-695
a compound having formula IV	CP-154,526
a compound having formula V	α-helical CRF 9-41
a compound having formula V	antalarmin
a compound having formula V	astressin
a compound having formula V	NBI 27914
a compound having formula V	R121919
a compound having formula V	R121920
a compound having formula V	antisauvagine-30
a compound having formula V	DMP-695
a compound having formula V	CP-154,526

[0463] By way of further example, Table 4b details a number of suitable combinations that may be employed in the methods and compositions of the present invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4b.

TABLE 4b

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	*α*-helical CRF 9-41

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	antalarmin

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	astressin

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	NBI 27914

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	R121919

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	R121920

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	antisauvagine-30

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	DMP-695

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	CP-154,526

[0464] By way of yet further example, Table 4c details additional suitable combinations that may be employed in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4c.

TABLE 4c

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
Celecoxib	α-helical CRF 9-41
Celecoxib	antalarmin
Celecoxib	astressin
Celecoxib	NBI 27914
Celecoxib	R121919
Celecoxib	R121920
Celecoxib	antisauvagine-30
Celecoxib	DMP-695
Celecoxib	CP-154,526
Cimicoxib	α-helical CRF 9-41
Cimicoxib	antalarmin
Cimicoxib	astressin
Cimicoxib	NBI 27914
Cimicoxib	R121919
Cimicoxib	R121920
Cimicoxib	antisauvagine-30
Cimicoxib	DMP-695
Cimicoxib	CP-154,526
Deracoxib	α-helical CRF 9-41
Deracoxib	antalarmin
Deracoxib	astressin
Deracoxib	NBI 27914
Deracoxib	R121919
Deracoxib	R121920
Deracoxib	antisauvagine-30
Deracoxib	DMP-695
Deracoxib	CP-154,526
Valdecoxib	α-helical CRF 9-41
Valdecoxib	antalarmin
Valdecoxib	astressin
Valdecoxib	NBI 27914
Valdecoxib	R121919
Valdecoxib	R121920
Valdecoxib	antisauvagine-30
Valdecoxib	DMP-695
Valdecoxib	CP-154,526
Rofecoxib	α-helical CRF 9-41
Rofecoxib	antalarmin
Rofecoxib	astressin
Rofecoxib	NBI 27914
Rofecoxib	R121919
Rofecoxib	R121920
Rofecoxib	antisauvagine-30
Rofecoxib	DMP-695
Rofecoxib	CP-154,526
Etoricoxib	α-helical CRF 9-41

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
Etoricoxib	antalarmin
Etoricoxib	astressin
Etoricoxib	NBI 27914
Etoricoxib	R121919
Etoricoxib	R121920
Etoricoxib	antisauvagine-30
Etoricoxib	DMP-695
Etoricoxib	CP-154,526
Meloxicam	α-helical CRF 9-41
Meloxicam	antalarmin
Meloxicam	astressin
Meloxicam	NBI 27914
Meloxicam	R121919
Meloxicam	R121920
Meloxicam	antisauvagine-30
Meloxicam	DMP-695
Meloxicam	CP-154,526
Parecoxib	α-helical CRF 9-41
Parecoxib	antalarmin
Parecoxib	astressin
Parecoxib	NBI 27914
Parecoxib	R121919
Parecoxib	R121920
Parecoxib	antisauvagine-30
Parecoxib	DMP-695
Parecoxib	CP-154,526
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	α-helical CRF 9-41
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	antalarmin
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	astressin
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	NBI 27914
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	R121919
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	R121920
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	antisauvagine-30

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	DMP-695
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	CP-154,526
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	α-helical CRF 9-41
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	antalarmin
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	astressin
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	NBI 27914
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	R121919
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	R121920
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	antisauvagine-30
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	DMP-695
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	CP-154,526
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	α-helical CRF 9-41
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	antalarmin
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	astressin
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	NBI 27914
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	R121919

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	R121920
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	antisauvagine-30
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	DMP-695
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	CP-154,526
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	α-helical CRF 9-41
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	antalarmin
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	astressin
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	NBI 27914
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	R121919
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	R121920
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	antisauvagine-30
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	DMP-695
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	CP-154,526

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	α-helical CRF 9-41
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	antalarmin
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	astressin
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	NBI 27914
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	R121919
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	R121920
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	antisauvagine-30
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	DMP-695
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	CP-154,526
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	α-helical CRF 9-41
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	antalarmin
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	astressin
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	NBI 27914
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	R121919
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	R121920
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	antisauvagine-30

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	DMP-695
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	CP-154,526
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	α-helical CRF 9-41
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	antalarmin
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	astressin
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	NBI 27914
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	R121919
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	R121920
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	antisauvagine-30
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	DMP-695
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	CP-154,526
Lumiracoxib	α-helical CRF 9-41
Lumiracoxib	antalarmin
Lumiracoxib	astressin
Lumiracoxib	NBI 27914
Lumiracoxib	R121919
Lumiracoxib	R121920
Lumiracoxib	antisauvagine-30
Lumiracoxib	DMP-695
Lumiracoxib	CP-154,526

DIAGNOSIS OF A VASO-OCCLUSION

[0100] One aspect of the invention encompasses diagnosing a subject in need of treatment or prevention for a vaso-occlusive event. A number of suitable methods for diagnosing a vaso-occlusion may be used in the practice of the invention.

In one such method, ultrasound may be employed. This method examines the blood flow in the major arteries and veins in the arms and legs with the use of ultrasound (high-frequency sound waves). In one embodiment, the test may combine Doppler® ultrasonography, which uses audio measurements to "hear" and measure the blood flow and duplex ultrasonography, which provides a visual image. In an alternative embodiment, the test may utilize multifrequency ultrasound or multifrequency transcranial Doppler® (MTCD) ultrasound.

Another method that may be employed encompasses injection of the subject with a compound that can be imaged. In one alternative of this embodiment, a small amount of radioactive material is injected into the subject and then standard techniques that rely on monitoring blood flow to detect a blockage, such as magnetic resonance direct thrombus imaging (MRDTI), may be utilized to image the vaso-occlusion. In an alternative embodiment, ThromboView® (commercially available from Agenix Limited) uses a clot-binding monoclonal antibody attached to a radiolabel. In addition to the methods identified herein, a number of other suitable methods known in the art for diagnosis of vaso-occlusive events may be utilized.

INDICATIONS TO BE TREATED

[0465] Typically, the composition comprising a therapeutically effective amount of a cyclooxygenase-2 selective inhibitor and a therapeutically effective amount of a corticotropin releasing factor antagonist may be employed to treat a number of ischemic mediated central nervous system disorders or injuries.

[0466] In some aspects, the invention provides a method to treat a central nervous system cell to prevent damage in response to a decrease in blood flow to the cell. Typically the severity of damage that may be prevented will depend in large part on the degree of reduction in blood flow to the cell and the duration of the reduction. By way of example, the normal amount of perfusion to brain gray matter in humans is about 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs when the flow of blood falls below approximately 8-10 mL/100 g of brain tissue/min, while at slightly higher levels (i.e. 20-35 mL/100 g of brain tissue/min) the tissue remains alive but not able to function. In one embodiment, apoptotic or necrotic cell death may be prevented. In still a further embodiment, ischemic-mediated damage, such as cytoxic edema or central nervous system tissue anoxemia, may be prevented. In each embodiment, the central nervous system cell may be a spinal cell or a brain cell.

[0467] Another aspect encompasses administrating the composition to a subject to treat a central nervous system ischemic condition. A number of central nervous system ischemic conditions may be treated by the composition of the invention. In one embodiment, the ischemic condition is a stroke that results in any type of ischemic central nervous system damage, such as apoptotic or necrotic cell death, cytoxic edema or central nervous system tissue anoxemia. The stroke may impact any area of the brain or be caused by any etiology commonly known to result in the occurrence of a stroke. In one alternative of this embodiment, the stroke is a brain stem stroke. Generally speaking, brain stem strokes strike the brain stem, which control involuntary life-support functions such as breathing, blood pressure, and heartbeat. In another alternative of this embodiment, the stroke is a cerebellar stroke. Typically, cerebellar strokes impact the cerebellum area of the brain, which controls balance and coordination. In still another embodiment, the stroke is an embolic stroke. In general terms, embolic strokes may impact any region of the brain and typically result from the blockage of an artery by a vaso-occlusion. In yet another alternative, the stroke may be a hemorrhagic stroke. Like embolic strokes, hemorrhagic stroke may impact any region of the brain, and typically result from a ruptured blood vessel characterized by a hemorrhage (bleeding) within or surrounding the brain. In a further embodiment, the stroke is a thrombotic stroke. Typically, thrombotic strokes result from the blockage of a blood vessel by accumulated deposits.

[0468] In another embodiment, the ischemic condition may result from a disorder that occurs in a part of the subject's body outside of the central nervous system, but yet still causes a reduction in blood flow to the central nervous system. These disorders may include, but are not limited to a peripheral vascular disorder, a venous thrombosis, a pulmonary embolus, a myocardial infarction, a transient ischemic attack, unstable angina, or sickle cell anemia. Moreover, the central nervous system ischemic condition may occur as result of the subject undergoing a surgical procedure. By way of example, the subject may be undergoing heart surgery, lung surgery, spinal surgery, brain surgery, vascular surgery, abdominal surgery, or organ transplantation surgery. The organ transplantation surgery may include heart, lung, pancreas or liver transplantation surgery. Moreover, the central nervous system ischemic condition may occur as a result of a trauma or injury to a part of the subject's body outside the central nervous system. By way of example, the trauma or injury may cause a degree of bleeding that significantly reduces the total volume of blood in the subject's body.

Because of this reduced total volume, the amount of blood flow to the central nervous system is concomitantly reduced. By way of further example, the trauma or injury may also result in the formation of a vaso-occlusion that restricts blood flow to the central nervous system.

[0469] Of course it is contemplated that the composition may be employed to treat the central nervous system ischemic condition irrespective of the cause of the condition. In one embodiment, the ischemic condition results from a vaso-occlusion. The vaso-occlusion may be any type of occlusion, but is typically a cerebral thrombosis or a cerebral embolism. In a further embodiment, the ischemic condition may result from a hemorrhage. The hemorrhage may be any type of hemorrhage, but is generally a cerebral hemorrhage or a subararachnoid hemorrhage. In still another embodiment, the ischemic condition may result from the narrowing of a vessel. Generally speaking, the vessel may narrow as a result of a vasoconstriction such as occurs during vasospasms, or due to arteriosclerosis. In yet another embodiment, the ischemic condition results from an injury to the brain or spinal cord.

[0470] In yet another aspect, the composition is administered to reduce infarct size of the ischemic core following a central nervous system ischemic condition. Moreover, the composition may also be beneficially administered to reduce the size of the ischemic penumbra or transitional zone following a central nervous system ischemic condition

[0471] In a further aspect, the invention provides treatment for subjects who are at risk of a vaso-occlusive event. These subjects may or may not have had a previous vaso-occlusive event. The invention embraces the treatment of subjects prior to a vaso-occlusive event, at a time of a vaso-occlusive event and following a vaso-occlusive event. Thus, as used herein, the "treatment" of a subject is intended to embrace both prophylactic and therapeutic treatment, and can be used either to limit or to eliminate altogether the symptoms or the occurrence of a vaso-occlusive event.

[0472] In addition to a cyclooxygenase-2 selective inhibitor and a corticotropin releasing factor antagonist, the composition of the invention may also include any agent that ameliorates the effect of a reduction in blood flow to the central nervous system. In one embodiment, the agent is an anticoagulant including thrombin inhibitors such as heparin and Factor Xa inhibitors such as warafin. In an additional embodiment, the agent is an anti-platelet inhibitor such as a GP IIb/IIIa inhibitor. In a further embodiment, the agent is selected from tissue plasminogen activator (t-PA), streptokinase, and

urokinase. Additional agents include but are not limited to, HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, and gemfibrizol; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); ß-adrenergic receptor blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

[0473] In a further aspect, the composition may be employed to reverse or lessen central nervous system cell damage following a traumatic brain or spinal cord injury. Traumatic brain or spinal cord injury may result from a wide variety of causes including, for example, blows to the head or back from objects; penetrating injuries from missiles, bullets, and shrapnel; falls; skull fractures with resulting penetration by bone pieces; and sudden acceleration or deceleration injuries. The composition of the invention may be beneficially utilized to treat the traumatic injury irrespective of its cause.

EXAMPLES

[0474] The following examples are intended to provide illustrations of the application of the present invention. The following examples are not intended to completely define or otherwise limit the scope of the invention.

EXAMPLE 1 - EVALUATION OF COX-1 AND COX-2 ACTIVITY *IN VITRO*

[0475] The COX-2 inhibitors suitable for use in this invention exhibit selective inhibition of COX-1 over COX-2, as measured by IC_{50} values when tested *in vitro* according to the following activity assays.

PREPARATION OF RECOMBINANT COX BACULOVIRUSES

[0476] Recombinant COX-1 and COX-2 are prepared as described by Gierse et al, [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 is cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus

transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses are isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells ($2x10^8$) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses are purified by three rounds of plaque purification and high titer (10^7-10^8 pfu/mL) stocks of virus are prepared. For large scale production, SF9 insect cells are infected in 10 liter fermentors (0.5 x 106/mL) with the recombinant baculovirus stock such that the multiplicity of infection is 0.1. After 72 hours the cells are centrifuged and the cell pellet is homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate is centrifuged at 10,000xG for 30 minutes, and the resultant supernatant is stored at -80°C before being assayed for COX activity.

ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0477] COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten minutes at 37°C by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

FAST ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0478] COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 µM phenol, 1 µM heme, 300 µM epinephrine) with the addition of 20 µl of 100 µM arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10 minutes at 25°C prior to the addition of arachidonic

acid. Any reaction between the arachidonic acid and the enzyme is stopped after two minutes at 37°C by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. Indomethacin, a non-selective COX-2/COX-1 inhibitor, may be utilized as a positive control. The PGE_2 formed is typically measured by standard ELISA technology utilizing a PGE2 specific antibody, available from a number of commercial sources.

[0479] Each compound to be tested may be individually dissolved in 2 ml of dimethyl sulfoxide (DMSO) for bioassay testing to determine the COX-1 and COX-2 inhibitory effects of each particular compound. Potency is typically expressed by the IC_{50} value expressed as g compound/ml solvent resulting in a 50% inhibition of PGE2 production. Selective inhibition of COX-2 may be determined by the IC_{50} ratio of COX-1/COX-2.

[0480] By way of example, a primary screen may be performed in order to determine particular compounds that inhibit COX-2 at a concentration of 10 ug/ml. The compound may then be subjected to a confirmation assay to determine the extent of COX-2 inhibition at three different concentrations (e.g., 10 ug/ml, 3.3 ug/ml and 1.1 ug/ml). After this screen, compounds can then be tested for their ability to inhibit COX-1 at a concentration of 10 ug/ml. With this assay, the percentage of COX inhibition compared to control can be determined, with a higher percentage indicating a greater degree of COX inhibition. In addition, the IC_{50} value for COX-1 and COX-2 can also be determined for the tested compound. The selectivity for each compound may then be determined by the IC_{50} ratio of COX-1/COX-2, as set-forth above.

EXAMPLE 2

[0481] In the examples below, a combination therapy contains a corticotropin releasing factor antagonist with a vehicle and a COX-2 selective inhibitor. The efficacy of such combination therapy can be evaluated in comparison to a control treatment such as a placebo treatment, administration of a COX-2 inhibitor only, or administration of a corticotropin releasing factor antagonist only. By way of example, a combination therapy may contain α-helical CRF 9-41 and celecoxib, α-helical CRF 9-41 and valdecoxib, α-helical CRF 9-41 and rofecoxib, or α-helical CRF 9-41 and paracoxib. In addition, any of the above mentioned COX-2 selective inhibitors may be similarly combined with other CRF antagonists, both peptide and non-peptide, such as for example, the pyrrolopyrimidines disclosed in WO 94/13676, CP-154,526 (Schulz et. al.,

Proc. Natl. Acad. Sci. USA, Vol. 93 (1996) 10477-10482), [D-phe^{12},Nle^{21,38}]hCRF-(12-14) (Gulyas et al., *Proc. Natl. Acad. Sci. USA*, Vol 92 (1995) 10575-10579), D-phe CRF (12-14) (Lyons et al. (1991)), astressin (Gulyas et al., *Proc. Natl. Acad. Sci. USA*, Vol 92 (1995) 10575-10579), and antalarmin (Webster et al., *Endocrinology*, Vol. 137 (1996) 57475750), NBI 27914 (Chen et al., J Med. Chem. 39: 4358-4360 (1996)), R121919, R121920 (7-dipropylamino)-2,5-dimethyl-3-[2-(dimethylamino)-5-pyridyl] pyrazolo [1,5-a] pyrimidine) (Mackay et al. (2001)), and other CFR antagonists known in the art, including the monocyclic five membered and six membered ring antagonists, and antagonists from the fused bicyclic, fused tricyclic, polycyclic, and acyclic systems.

[0482] It should be noted that these are only several examples, and that any CFR antagonist in combination with any COX-2 inhibitor of the present invention may be tested as a combination therapy. The dosages of a CFR antagonist and COX-2 inhibitor in a particular therapeutic combination may be readily determined by a skilled artisan conducting the study. The length of the study treatment will vary on a particular study and can also be determined by one of ordinary skill in the art. The combination therapy may be administered for any time period necessary to treat the ischemic event. By way of example, the combination therapy may be administered for 12 weeks. The CFR antagonist and COX-2 inhibitor can be administered by any route as described herein, but are preferably administered orally or intravenously for human subjects.

[0483] The laboratory animal study can generally be performed as described in Strijbos, et al., (1994) *Brain Research*, 656: 405-408.

[0484] Briefly, the study can be performed on male, Sprague-Dawley rats ranging in size from 200 to 250 g. The rats are anesthetized with sodium pentobarbitone, and guide cannulae are implanted into the third ventricle of the brain. This is performed seven days prior to ischemia. At least four days later, the rats are subjected to a unilateral, permanent middle cerebral artery occlusion ("MCAo") under halothane anesthesia (2% in oxygen) by electrocoagulation according to a modification of the technique disclosed in Tamura et al. ((1981) *J. Cereb. Blood Flow Metab.*, 1: 53-60).Body temperature is maintained during surgery using a heated blanket.

[0485] Rats are then injected with either a vehicle (0.9% saline) or a corticotropin releasing hormone antagonist, such as, for example, α-helical CRF 9-41 (6.5 mmol; total volume 2 µl) both 30 minutes before and 10 minutes after the MCAo.

[0486] The brain tissue can then be examined histologically for the effects of combination therapy in comparison to the placebo. Neuronal damage is determined

histologically 24 hours after ischemia. 500 µm coronal brain slices are incubated with tetrazolium stain, a histological indicator of mitochondrial viability. Lesion size is then quantified by automated Seescan image analysis.

EXAMPLE 3

[0487] This laboratory animal study can generally be performed as described in Lyons, et al., (1991) *Brain Research*, 545: 339-342.

[0488] Male Winstar rats weighing 250-300 g are induced with 2.0% halothane, intubates, and ventilated with 1.0% halothane. PE-50 catheters are inserted into the femoral vein and artery, Core body temperature is monitored and maintained at 37.0± 0.5 °C. An intraventricular injection of α-helical CRF 9-41 is administered 0.80 mm posterior, 1.50 mm lateral to the bregma and 3.80 mm deep. Fifteen minutes after injection, transient forebrain ischemia is produced for a 10 minute period by the temporary occlusion of both common carotid arteries and phlebotomizing the rat to a MABP of 50 mm Hg. After 10 minutes of ischemia, previously withdrawn and heparinized blood was infused via the femoral venous catheter and cerebral blood flow is restored by removal of the carotid artery clips. Animals are then monitored under 1.0% halothane for a 1 hour period after reperfusion (restoration of carotid blood flow).

[0489] Seven groups of five animals each are studied. Three groups act as control groups: one normal control group, one ischemic control group, and one ischemic vehicle group. The remaining four groups receive α-helical CRF 9-41 in doses of 0.1, 1.0, 10.0, or 100.0 µg in 0.9 & BaCl, the volume of each injection being 5 µl. Arterial blood samples are taken and MABP is observed and recorded as follows: 10 minutes prior to injection of α-helical CRF 9-41; after 10 minutes of ischemia just prior to reperfusion; and 30 minutes following reperfusion.

[0490] Seven days post-op, each rat is anesthetized with 2.0% halothane and the brain fixed *in situ* with 40% formaldehyde/glacial acetic acid/methanol, 1:1:8 via transcardiac perfusion after briefly washing out the cephalic circulation with heparinized 0.9% NaCl for 45 seconds. The brains are then sectioned 7mm posterior to the rostral tip of the frontal lobes and 10µm paraffin sections are stained using hematoxylin and eosin. Hippocampal regions CA1-medial, CA1-lateral, CA3, and CA4 are examined bilaterally under light microscopy using an ocular grid with magnification X 400. Ten 100 X 100 µm area are analyzed in each hippocampal region. Neurons displaying a normal nucleus, cytoplasmic staining, and configuration are counted as living cells, as

opposed to pyknotic, hyperchromatic, and shrunken neurons that would be counted as dead cells.

[0491] The number of surviving neurons and dead neurons are compared to determine the efficacy of the combination therapy. Furthermore, the $PaCO_2$, PaO_2, pH_a, MABP, serum glucose, and core body temperatures among the rats representing the various control and experimental groups are compared to determine possible side effects of the therapy or the procedures used.

EXAMPLE 4

[0492] This laboratory animal study can generally be performed as described in Mackay et al., (2001) *J. Cerebral Blood Flow and Metabolism* 21:1208-1214.

[0493] Brain and plasma levels of R121920 are determined in a number of nonoccluded male Sprague–Dawley rats weighing 280 to 340 g. A skilled artisan can readily determine the appropriate number of animals to be used for a particular experiment. R121920 in a vehicle of water is administered to each of the rats as a single intravenous (IV) dose of 10 mg/kg. An equal number of the rats are killed at 2, 5, 15, 30, 60, 120, and 240 minutes subsequent to the administration of R121920. Brains are rapidly removed, flash frozen in liquid nitrogen, and stored at -70°C until analysis. 200 μL terminal blood samples are collected into tubes containing EDTA and are promptly centrifuged for 1.5 minutes at 10,000 g. The plasma is extracted, flash frozen in liquid nitrogen, and stored at –70°C until analysis. In order to quantify the concentration of R121920 in plasma, 150 μL acetonitrile is added to 50 μL plasma to precipitate protein, and the sample is centrifuged. The supernatant is collected and dried in a Speed Vac at room temperature. In order to prepare brain sample tissue, brain tissue is homogenized in 1 mL saline solution. Protein is precipitated by adding 3 vol acetonitrile to the sample solution. After reconstitution, all samples are analyzed in a reverse phase HPLC-UV system. The concentrations of R121920 in the samples is predicted from the linear regression of an external calibration curve of five spiked matrix standards.

[0494] All rats are initially anesthetized with a mixture of 5% halothane, 30% oxygen, and 70% nitrous oxide in an induction chamber and maintained thereafter with a nitrous oxide/oxygen mixture (70%:30%) containing 1.0% to 1.5% halothane administered through a face mask. Body temperature is monitored during the surgical

procedure by a rectal thermometer. The rats are maintained at a normothermic body temperature (37 °C ± 1°C) by use of a heating blanket controlled by the thermometer.

SUBTEMPORAL MIDDLE CEREBRAL ARTERY OCCLUSION MODEL

[0495] Permanent focal ischemia is induced in male Fischer 344 rats (240 to 280 g) through a subtemporal approach, as described in Tamara et al., (1981) *J. Cereb. Blood Flow Metab.* 1: 53-60. Briefly, the craniectomy is performed at the level where the MCA crosses the lateral olfactory tract. The dura is opened, and the artery is exposed and occluded by bipolar diathermy from its origin to the point where it crosses the inferior cerebral vein. All visible lenticulostriate branches are also occluded. The artery is transected to confirm complete occlusion and to prevent recanalization. The incision sites are closed, and the animals are allowed to recover from the anesthesia.

[0496] R121920 (10 mg/kg or 20 mg/kg) is administered as an initial bolus IV dose at the time of the onset of ischemia, followed by subsequent subcutaneous (SC) injections of R121920 (5 mg/kg or 10mg/kg, respectively) at hourly intervals thereafter for a period of 4 hours. Control rats are injected with a water vehicle (1 mL/kg) at the same time points.

[0497] The rats are killed 24 hours subsequent to MCA occlusion, the brains are removed, and 500 μm coronal sections are cut from the frontal pole on a vibratome. Brain sections are incubated in a 2% solution of triphenyl tetrazolium chloride at 37°C for 30 minutes to stain for viable tissue. Infarcted regions in the hemisphere, the cortex, and the striatum on each of the sections are delineated and transcribed onto scale diagrams and quantified by automated image analysis. The infarct volume for each of the brain regions is computed by summing the areas of damage from each section and multiplying them by the distance between the sections.

INTRALUMINAL SUTURE MIDDLE CEREBRAL ARTERY OCCLUSION MODEL.

[0498] The left middle cerebral artery (MCA) is permanently occluded in a number of male Sprague-Dawley rats weighing 280 to 340 g through a cervical carotid approach using the intraluminal suture technique in male as described in detail in Zea Longa et al., (1989) *Stroke* 20: 84-91. Briefly, the common carotid, the external carotid, and the internal carotid arteries are exposed via a midline cervical incision performed under an operating microscope. A 30-mm length of 3–0 monofilament nylon suture with tip heat-blunted and coated with poly-l-lysine solution (Belayev et al.,(1996) *Stroke* 27:

1616-1622) is advanced from the external carotid artery into the lumen of the internal carotid artery until mild resistance is felt (typically 19 to 20 mm depending upon the body weight of the rat), resulting in the occlusion of the origin of the MCA. After closure of the incision, the rats are allowed to recover from anesthesia.

[0499] R121920 (10 mg/kg) is administered as an IV injection at the time of MCA occlusion, followed by additional IV injections of R121920 (10 mg/kg) at 1, 2, 3 and 4 hours subsequent thereto. Control rats are injected with a water vehicle at the same time points. The period of neuroprotective effect of R121920 is examined by delaying induction of the dosing regimen to 0, 0.5, and 1 hour after occlusion of the MCA.

[0500] Twenty-four hours subsequent to MCA occlusion, the rats are killed and the brains are removed and frozen in isopentane at –40°C. Brains are cut into 20-μm serial coronal sections at 12 equidistant levels (1 mm apart, covering the entire forebrain), are fixed for 10 minutes in 4% paraformaldehyde, and are stained with hematoxylin and eosin. The sections, corresponding to 12 stereotactically predetermined coronal planes of the brain from anterior +12.7 mm to anterior +1.7 mm relative to the interaural line (Paxinos and Watson, *The rat brain in stereotaxic coordinates*. San Diego, CA: Academic Press), are examined using a light microscope. Areas of ischemic damage are delineated and transcribed onto scale diagrams of a normal forebrain at each of the 12 coronal planes. Infarcted areas are quantified using a computer-based image analysis system, and the total volumes of ischemic tissue for each brain are derived from integration of the areas of damage in the 12 planes and the known stereotactic coordinates of the planes. The volumes of the cerebral hemispheres ipsilateral and contralateral to the occluded MCA are determined from the stained histologic sections by assessment of the total surface area at the same coronal planes as used for assessing areas of ischemic damage. The difference between the two hemispheres provide a measure of brain swelling.

[0501] It should be noted that all of the above-mentioned procedures can be modified for a particular study, depending on factors such as a drug combination used, length of the study, subjects that are selected, etc. Such modifications can be designed by a skilled artisan without undue experimentation.

WHAT IS CLAIMED IS:

1. A method for treating a stroke, the method comprising:

(a) diagnosing a subject in need of treatment for a stroke; and

(b) administering to the subject a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a corticotropin releasing factor antagonist or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

2. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

3. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

4. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, meloxicam, parecoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid, (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

5. The method of claim 1 wherein the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

6. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist are administered substantially simultaneously.

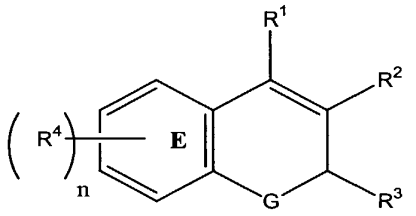
7. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist are administered sequentially.

8. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is administered to the subject in an amount of about 0.1 to about 20 mg/kg body weight per day.

9. The method of claim 1 wherein the corticotropin releasing factor antagonist is administered to the subject in an amount of about 1 to about 50 milligrams per kilogram of the subject's weight per day.

10. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof having the formula:



(I)

wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is O, S or NR^a;

R^a is alkyl;

R^1 is selected from the group consisting of H and aryl;

R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

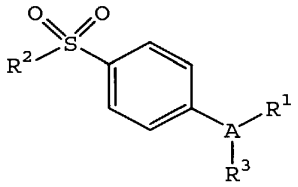
each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl,

heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of *α*-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

11. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof of the formula:



wherein:

A is selected from the group consisting of a partially unsaturated or unsaturated heterocyclyl ring and a partially unsaturated or unsaturated carbocyclic ring;

R^1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^2 is selected from the group consisting of methyl and amino; and

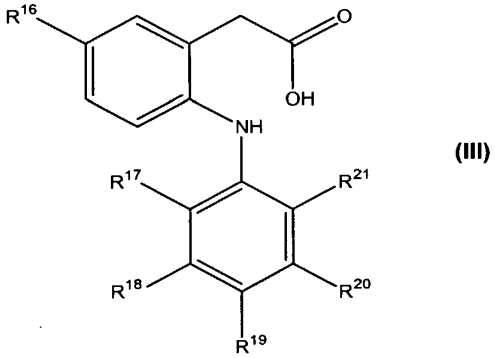
R^3 is selected from the group consisting of H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl,

alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,
N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of *α*-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

12. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof having the formula:



(III)

wherein:

R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl, provided, however, that each of R^{17}, R^{18}, R^{20} and R^{21} is not fluoro when R^{16} is ethyl and R^{19} is H; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

13. A composition comprising a cyclooxygenase-2 selective inhibitor selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, parecoxib, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, and a corticotropin releasing factor antagonist selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

14. The composition of claim 13 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, and parecoxib, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, and the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

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(71) Applicant: **SPRUCE BIOSCIENCES, INC.** [US/US]; 548 Market Street, Suite 74589, San Francisco, California 94105 (US).

(72) Inventors: **GHOSH, Sangita**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US). **BARNES, Christopher**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US). **HUANG, Michael**; 548 Market Street, Suite 74589, San Francisco, California 94105 (US).

(74) Agent: **LAMIQUIZ, Jiarong L.**; WILSON SONSINI, 650 Page Mill Road, Palo Alto, California 94304 (US).

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(54) Title: METHODS OF TREATING CONGENITAL ADRENAL HYPERPLASIA

(57) Abstract: Patients with congenital adrenal hyperplasia (CAH) need adequate care and treatment in order to lead normal lives. Hence, there is a need for new methods of treating CAH. This disclosure provides new compounds, salts, compositions and uses thereof in the treatment of CAH.

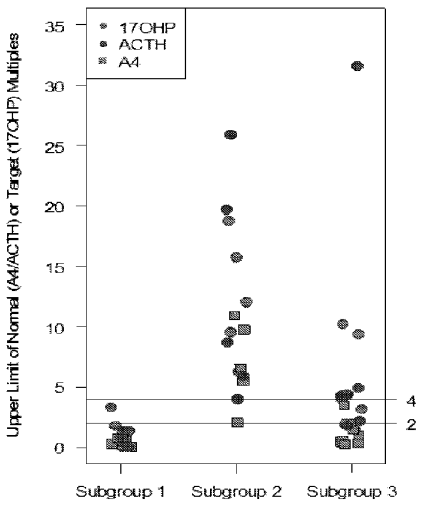

FIG. 1

[Continued on next page]

WO 2021/016208 A1

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— *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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METHODS OF TREATING CONGENITAL ADRENAL HYPERPLASIA

CROSS-REFERENCE

[0001] This application claims priority to U.S. Provisional Patent Application No 62/876,176, filed July 19, 2019, and U.S. Provisional Patent Application No 63/047,822, filed on July 2, 2020, each of which is entirely incorporated herein by reference.

BACKGROUND

[0002] Congenital adrenal hyperplasia (CAH) is a group of rare inherited autosomal recessive disorders characterized by a deficiency of one of the enzymes needed to make specific hormones. CAH affects the adrenal glands located at the top of each kidney. Normally, the adrenal glands are responsible for producing three different hormones: 1) glucocorticoids, which gauge the body's response to stress, illness, or injury; 2) mineralocorticoids, which regulate salt and water levels; and 3) androgens, which are male sex hormones. An enzyme deficiency may make the body unable to produce one or more of these hormones, which in turn may result in the overproduction of another type of hormone precursor in order to compensate for the loss.

SUMMARY

[0003] Congenital Adrenal Hyperplasia (CAH) patients need adequate care and treatment in order to lead normal lives. Hence, there is a need for new methods of treating CAH. This disclosure provides new compounds, salts, compositions and uses thereof in the treatment of CAH.

[0004] In an aspect, the present disclosure provides methods for treating Congenital Adrenal Hyperplasia (CAH). The method comprises administering a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof to a subject, wherein when said subject has a level of at least one steroid hormone that is less than two times an upper limit of a reference range of said at least one steroid hormone level , a dose of said steroid or a pharmaceutically acceptable salt thereof is reduced compared to a dose of said steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient that does not receive said CRF_1 antagonist or a pharmaceutically acceptable salt thereof.

[0005] In some embodiments, the subject has a level of a second and different steroid hormone that is less than two times an upper limit of a reference range of said second and different steroid hormone level. In some embodiments, the steroid hormone is selected from the group consisting of adrenocorticotropic hormone (ACTH), androstenedione (A4), 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone,

aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, dehydroepiandrosterone, androstenediol, testosterone, dihydrotestosterone, estrone, estradiol, and estriol.

[0006] In some embodiments, the subject has a level of 17-OHP that is less than two times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than two times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than two times an upper limit of a reference range of 17-OHP and a level of A4 that is less than two times an upper limit of a reference range of A4. In some embodiments, the subject has a level of A4 that is less than two times an upper limit of a reference range of A4 and a level of ACTH that is less than two times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.75 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.75 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.75 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.75 times an upper limit of a reference range of A4. In some embodiments, the subject has a level of A4 that is less than 1.75 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.75 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.5 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.5 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.5 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.5 times an upper limit of a reference range of A4. In some embodiments, the subject has a level of A4 that is less than 1.5 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.5 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.25 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.25 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than 1.25 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.25 times an upper limit of a reference range of A4. In some embodiments, the subject has a level of A4 that is less than 1.25 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.25 times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than one times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than one times an upper limit of a reference range of ACTH. In some embodiments, the subject has a level of 17-OHP that is less than one times an upper limit of a reference range of 17-OHP and a level of A4 that is less than one times an upper limit of a reference range of A4. In some embodiments, the subject has a level of A4 that is less than one

times an upper limit of a reference range of A4 and a level of ACTH that is less than one times an upper limit of a reference range of ACTH.

[0007] In some embodiments, the methods comprise reducing said dose of said steroid or a pharmaceutically acceptable salt thereof in a 5 mg increment.

[0008] In another aspect, the present disclosure provides methods for treating Congenital Adrenal Hyperplasia (CAH). The methods comprise administering a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof to a subject, wherein when said subject has a level of at least one steroid hormone that is more than an upper limit of a reference range of said at least one steroid hormone level, a dose of said steroid or a pharmaceutically acceptable salt thereof is not reduced compared to a dose of said steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient that does not receive said CRF1 antagonist or a pharmaceutically acceptable salt thereof.

[0009] In some embodiments, the subject has a level of said at least one steroid hormone that is more than two times an upper limit of a reference range of said at least one steroid hormone level. In some embodiments, the subject has a level of said at least one steroid hormone that is more than 1.75 times an upper limit of a reference range of said at least one steroid hormone level. In some embodiments, the subject has a level of said at least one steroid hormone that is more than 1.5 times an upper limit of a reference range of said at least one steroid hormone level. In some embodiments, the subject has a level of said at least one steroid hormone that is more than 1.25 times an upper limit of a reference range of said at least one steroid hormone level.

[0010] In some embodiments, the steroid hormone is selected from the group consisting of adrenocorticotropic hormone (ACTH), androstenedione (A4), 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, dehydroepiandrosterone, androstenediol, testosterone, dihydrotestosterone, estrone, estradiol, and estriol.

[0011] In some embodiments, the methods further comprise maintaining said dose of said steroid or a pharmaceutically acceptable salt thereof until said levels of at least two steroid hormones are less than 2 times said upper limit of said reference ranges of said two steroid hormones respectively. In some embodiments, the methods further comprise reducing said dose of said steroid or a pharmaceutically acceptable salt thereof in a 5 mg increment when said levels of at least two steroid hormones are less than 2 times said upper limit of said reference ranges of said two steroid hormones respectively.

[0012] In some embodiments, the at least two steroid hormones comprise 17-OHP and ACTH. In some embodiments, the at least two steroid hormones comprise 17-OHP and A4. In some embodiments, the at least two steroid hormones comprise A4 and ACTH. In some embodiments, the reference range of ACTH or A4 level of said subject is controlled by a factor selected from the group consisting of age, sex, menopausal status, laboratory setting, time of a day and combinations thereof.

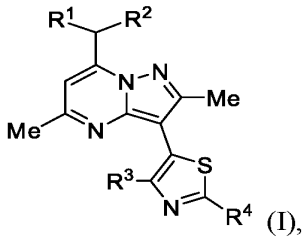
[0013] In some embodiments, the level of ACTH or A4 is 2 times, 1.5 times, 1.25 times, or 1 times said upper limit of said normal range of ACTH or A4 level of said subject. In some embodiments, the amount of said steroid or a pharmaceutically acceptable salt thereof comprises a range of about 10 mg to about 80 mg of hydrocortisone equivalents, wherein said steroid or a pharmaceutically acceptable salt thereof is administered daily. In some embodiments, the amount of said CRF_1 antagonist or a pharmaceutically acceptable salt thereof comprises a range of about 10 mg to about 200 mg, wherein said CRF_1 antagonist or a pharmaceutically acceptable salt thereof is administered daily.

[0014] In some embodiments, the subject is treated for a period of about 4 weeks to about 36 weeks.

[0015] In some embodiments, the subject is treated for a period of about 4 weeks to about 36 weeks, said subject is reassessed to determine if a different method of treating CAH should be administered.

[0016] In some embodiments, the CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003.

[0017] In some embodiments, the CRF_1 antagonist is a compound of Formula (I):

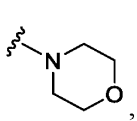
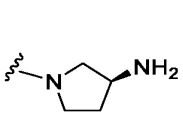
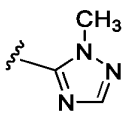
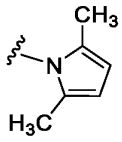


(I),

or a pharmaceutically acceptable salt thereof, wherein:

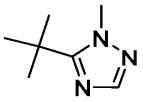
R^1 and R^2 are independently ethyl or *n*-propyl;

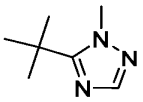
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

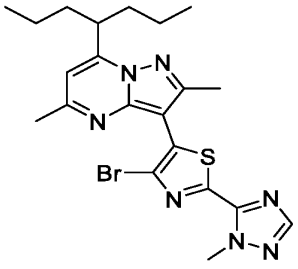
[0018] In some embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

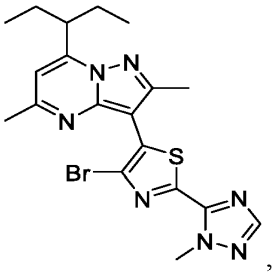
[0019] The method of claims 38 or 39, wherein R^3 is Cl, Br, or methyl.

[0020] In some embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  .

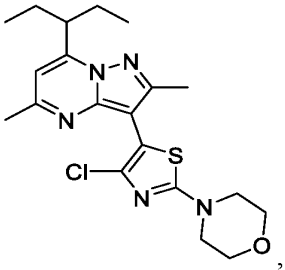
[0021] In some embodiments, R^4 is morpholin-4-yl or  .

[0022] In some embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

[0023] In some embodiments the compound is  , or a pharmaceutically acceptable salt thereof.

[0024] In some embodiments the compound is  , or a pharmaceutically acceptable salt thereof.

[0025] In some embodiments the compound is



, or a pharmaceutically acceptable salt thereof.

[0026] In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg to about 200 mg total daily dose to the subject.

[0027] In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject. In some embodiments, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject.

[0028] In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject.

[0029] In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm to about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μm.

[0030] In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

[0031] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

[0032] In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further

comprises one or more pharmaceutically acceptable excipients. In some embodiments, the steroid or pharmaceutically acceptable salt thereof is a glucocorticoid or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid or a pharmaceutically acceptable salt thereof is prednisone, cortisone, prednisolone, triamcinolone, methylprednisolone, betamethasone, dexamethasone, hydrocortisone or a pharmaceutically acceptable salt thereof. In some embodiments, the levels of steroid hormones in the subject are determined from a biological sample from the subject. In some embodiments, the biological sample is selected from the group of blood, blood fractions, plasma, serum, and saliva. In some embodiments, the biological sample is obtained non-invasively.

[0033] In some embodiments, the subject is tested in the morning. In some embodiments, subject is tested to determine morning levels of A4 and ACTH. In some embodiments, the subject is a pediatric patient. In some embodiments, the subject is from about newborn to about 18 years old.

[0034] In some embodiments, the subject is an adult patient. In some embodiments, the steroid and the CRF1 antagonist are administered concurrently. In some embodiments, the steroid and the CRF1 antagonist are administered in one pharmaceutical composition.

[0035] In some embodiments, the steroid and the CRF1 antagonist are administered concurrently in separate pharmaceutical compositions. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 24 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 8 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 2 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 10 minutes.

[0036] In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

[0037] In another aspects, the present disclosure provides compositions comprising a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof, wherein said CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is exogenous glucocorticoids (GC) or a pharmaceutically acceptable salt thereof.

[0038] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0039] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG."), of which:

[0041] FIG. 1 shows the baseline upper limit of a normal range (ULN)/Target Multiples for Serum 17-OHP, ACTH and A4 by subgroup;

[0042] FIGS. 2A and 2B illustrate a time matched change of ACTH hormone profile;

[0043] FIGS. 3A and 3B illustrate a time matched change of 17-OHP hormone profile; and

[0044] FIGS. 4A and 4B illustrate a time matched change of ACTH hormone profile.

DETAILED DESCRIPTION

[0045] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

Congenital adrenal hyperplasia

[0046] Congenital adrenal hyperplasia (CAH) is a group of rare inherited autosomal recessive disorders characterized by a deficiency of one of the enzymes needed to make specific hormones. CAH effects the adrenal glands located at the top of each kidney. Normally, the adrenal glands are responsible for producing three different hormones: 1) glucocorticoids, which gauge the body's response to stress, illness or injury; 2) mineralocorticoids, which regulate salt and water levels; and 3) androgens, which are male sex hormones. An enzyme deficiency will make the body unable to produce one or more of these hormones, which in turn will result in the overproduction of another type of hormone precursor in order to compensate for the loss.

[0047] The most common cause of CAH is the absence of the enzyme 21-hydroxylase. Different mutations in the gene responsible for 21-hydroxylase result in different levels of the enzyme, producing a spectrum of effects. CAH due to 21-hydroxylase deficiency is responsible for 95% of all cases of CAH and is broken down further into two subcategories: classic CAH, which can be sub-divided into the salt-losing form or the simple-virilizing form, and non-classic CAH. Classic CAH is by far the more severe form and can result in adrenal crisis and death if not detected and treated. Non-classic CAH is milder and may or may not present symptoms. Since the absence of 21-hydroxylase makes these individuals unable to make the hormone cortisol, a glucocorticoid, and, in the case of salt-losing CAH, aldosterone (a mineralocorticoid), the excess steroid precursors, namely 17-hydroxyprogesterone (17-OHP), build up and are shunted down the androgen pathway resulting in excess androgen production which cause a variety of symptoms such as abnormal genital development in infant girls. There are other much rarer forms of CAH as well, including 11-ß hydroxylase deficiency, 17α-hydroxylase deficiency, 3-ß-hydroxysteroid dehydrogenase deficiency, congenital lipoid adrenal hyperplasia and p450 oxidoreductase deficiency which all present different symptoms. CAH patients need adequate care and treatment in order to lead normal lives.

Corticotropin releasing factor

[0048] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

[0049] CRF has been implicated in psychiatric disorders and neurological diseases including depression and anxiety, as well as the following: Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol and substance abuse and associated withdrawal symptoms, obesity, metabolic syndrome, congenital adrenal hyperplasia (CAH), Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulceration, premenstrual syndrome, sexual dysfunction, premature labor, inflammatory disorders, allergies, multiple sclerosis, visceral pain, sleep disorders, pituitary tumors or ectopic pituitary derived tumors, chronic fatigue syndrome, and fibromyalgia.

[0050] CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain thereby suggesting potential functional diversity. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors.

[0051] Treatment of CAH is based on normalization of hormone and steroid levels using a variety of chronic medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous Cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which Cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment include cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

[0052] The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient cortisol is available during events that may elicit a strong stress response (e.g., intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of Addisonian syndrome due to under-treatment. Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione (A4), testosterone, renin activity, and electrolytes.

[0053] Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, absence of the nadir drop in systolic

blood pressure overnight, and insulin resistance. A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the aforementioned adverse outcomes. Treatment of CAH includes efforts to normalize the Cortisol deficiency with glucocorticoids (usually hydrocortisone in children and adults). In some embodiments, there is a need for longer acting and more potent agents with narrow therapeutic indices, such as dexamethasone or prednisolone/prednisone, in adults and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients.

[0054] CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotropic hormone ("ACTH"), β-endorphin, and other proopiomelanocortin ("POMC")-derived peptides from the anterior pituitary. Secretion of CRF causes release of ACTH from corticotrophs in the anterior pituitary via binding to the CRF1 receptor, a member of the class B family of G-protein coupled receptors.

[0055] Due to the physiological significance of CRF1, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF1 receptor remains a desirable goal and has been the subject of ongoing research and development for the treatment of anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse.

[0056] The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21-hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-OHP. Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione (A4), testosterone, and dihydroxytestosterone causing virilization in females. In addition, 21-hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically cortisol and aldosterone. Cortisol is a critical negative

feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

Certain Definitions

[0057] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

[0058] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

[0059] The term "about" is used to indicate that a value includes 10% level of error for the device or method being employed to determine the value.

[0060] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or."

[0061] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, and preferably having from one to five carbon atoms (i.e. C1-C5alkyl). In some embodiments, an alkyl comprises one to four carbon atoms (i.e., C1-C4alkyl).). In some embodiments, an alkyl comprises one to three carbon atoms (i.e., C1-C3alkyl).). In some embodiments, an alkyl comprises one to two carbon atoms (i.e., C1-C2alkyl). In some embodiments, an alkyl comprises one carbon atom (i.e., C1alkyl). In certain embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (n-propyl), 1-methylethyl (iso-propyl), 1-butyl (n-butyl), 1-methylpropyl (sec-butyl), 2-methylpropyl (isobutyl), 1,1-dimethylethyl (tert-butyl), or 1-pentyl (n-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more substituents such as those described herein.

[0062] The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that

"comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

[0063] "Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. "Administering" a pharmaceutical composition may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

[0064] By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

[0065] The term "pharmaceutical composition" means a composition comprising at least one active ingredient, such as a steroid or a pharmaceutically acceptable salt thereof or a CRF1 antagonist or a pharmaceutically acceptable salt thereof, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

[0066] The term "supraphysiologic amount" describes glucocorticoid dose levels that are above the daily glucocorticoid requirement (production rate) found in healthy individuals.

[0067] The term "physiologic amount" describes glucocorticoid dose levels that meet the daily glucocorticoid requirement (production rate) found in healthy individuals.

[0068] The term "hydrocortisone equivalents" as used herein is understood by a person skilled in the art to be the conversion calculations needed to be considered when substituting one glucocorticoid for another as the potency and duration of action of various glucocorticoids may vary. Hence, the term "hydrocortisone equivalents" is the standard used for comparison of glucocorticoid potency.

[0069] A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the

pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

[0070] The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

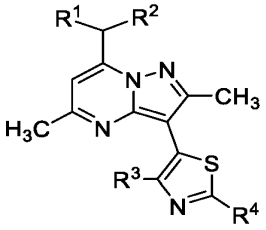
Compounds

[0071] Disclosed herein are CRF1 antagonists or pharmaceutically acceptable salt thereof such as Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003, and SSR125543.

[0072] In one aspect, the CRF1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: N-Butyl-N-ethyl-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine hydrochloride (Antalarmin hydrochloride), N-Butyl-N-ethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine hydrochloride (Pfizer CP154526), N-(1-Ethylpropyl)-3,6-dimethyl-2-(2,4,6-trimethylphenox y)-4-pyridinamine hydrochloride (Pfizer CP376395 hydrochloride), 5-Chloro-N-(cyclopropylmethyl)-2-methyl-N-propyl-N'-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride (NBI27914 hydrochloride), (7S)-6-(Cyclopropylmethyl)-2-(2,4-dichlorophenyl)-7-ethyl-7,8-dihydro-4-methyl-6H-1,3,6,8a-tetraazaacenaphthylene hydrochloride (NBI35965 hydrochloride), N-(1-Ethylpropyl)-3-methoxy-5-[2-methoxy-4-

(trifluoromethoxy)phenyl]-6-methyl-2-pyrazinamine hydrochloride (NGD 98-2 hydrochloride), 8-(6-Methoxy-2-methyl-3-pyridinyl)-2,7-dimethyl-N-[(1R)-1-methylpropyl]pyrazolo[1,5-a]-1,3,5-triazin-4-amine (Pexacerfont), 3-[6-(Dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-a]pyrimidin-7-amine hydrochloride (R 121919 hydrochloride), and N-(4-Methoxy-2-methylphenyl)-1-[1-(methoxymethyl)propyl]-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridine-4-amine (SN003), (S)-4-(2-chloro-4-methoxy-5-methylphenyl)-N-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-(prop-2-yn-1-yl)thiazol-2-amine (SSR125543).

[0073] Disclosed herein is a compound of Formula (I):



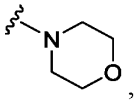
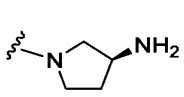
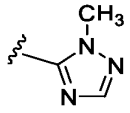
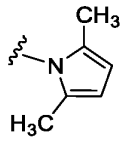
[0074]

[0075] Formula (I)

[0076] or a pharmaceutically acceptable salt thereof, wherein

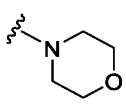
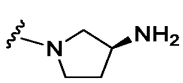
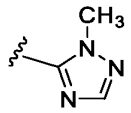
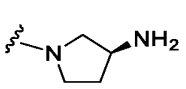
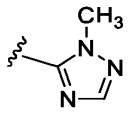
[0077] R1 and R2 are independently ethyl or n-propyl;

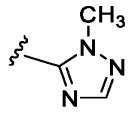
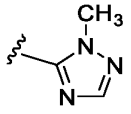
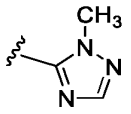
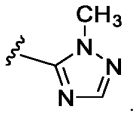
[0078] R3 is H, Cl, Br, methyl, trifluoromethyl or methoxy;

[0079] R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

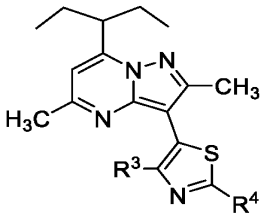
[0080] Ra and Rb are independently hydrogen, C1-C3 alkyl, H2NCH2CH2-, (CH3)3COC(O)NHCH2CH2-, or CH3CH2CH2NHCH2CH2.

[0081] In some embodiments, R3 is hydrogen, Cl, Br, methyl, or trifluoromethyl. In some embodiments, R3 is hydrogen, Cl, Br, or methyl. In some embodiments, R3 is hydrogen, Cl, or Br. In some embodiments, R3 is hydrogen. In some embodiments, R3 is Cl. In some embodiments, R3 is Br.

[0082] In some embodiments, R4 is hydrogen, Br, RaRbN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,or  . In some embodiments, R4 is Br, RaRbN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,or  . In some embodiments, R4 is RaRbN–, methoxymethyl, n-

butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R4 is RaRbN–, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R4 is RaRbN–,pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R4 is morpholin-4-yl or  . In some embodiments, R4 is RaRbN- and Ra and Rb are independently C1-C3alkyl.

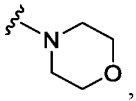
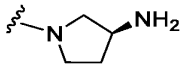
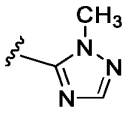
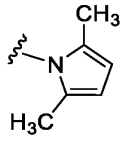
[0083] Disclosed herein is a compound of Formula (II):



[0084] Formula (II)

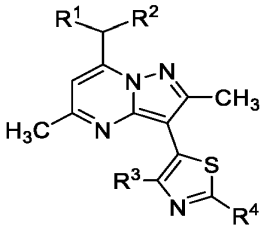
[0085] or a pharmaceutically acceptable salt thereof, wherein

[0086] R3 is H, Cl, Br, methyl, trifluoromethyl or methoxy;

[0087] R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

[0088] Ra and Rb are independently hydrogen, C1-C3 alkyl, H2NCH2CH2-, (CH3)3COC(O)NHCH2CH2-, or CH3CH2CH2NHCH2CH2.

[0089] Disclosed herein is a compound of Formula (III):

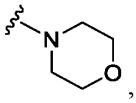
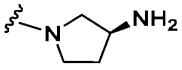
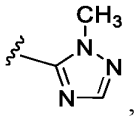
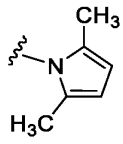


[0090] Formula (III)

[0091] or a pharmaceutically acceptable salt thereof, wherein

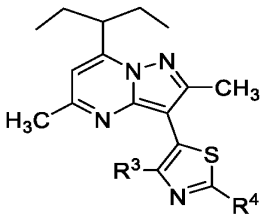
[0092] R1 and R2 are n-propyl;

[0093] R3 is H, Cl, Br, methyl, trifluoromethyl or methoxy;

[0094] R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

[0095] Ra and Rb are independently hydrogen, C1-C3 alkyl, H2NCH2CH2-, (CH3)3COC(O)NHCH2CH2-, or CH3CH2CH2NHCH2CH2.

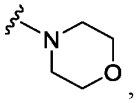
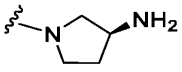
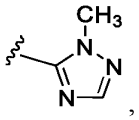
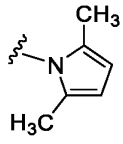
[0096] Disclosed herein is a compound of Formula (IV):



[0097] Formula IV

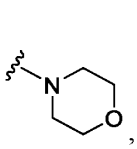
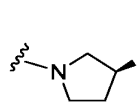
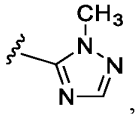
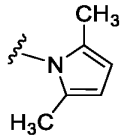
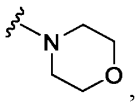
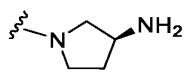
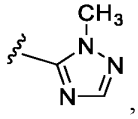
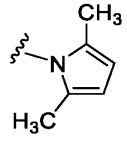
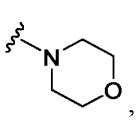
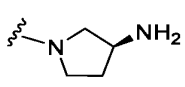
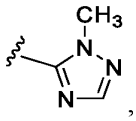
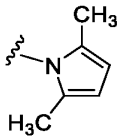
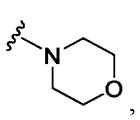
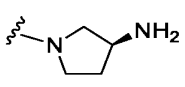
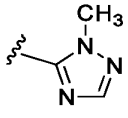
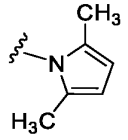
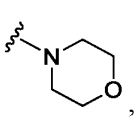
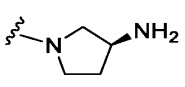
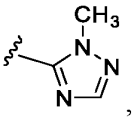
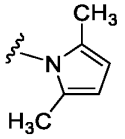
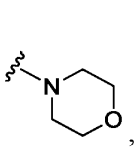
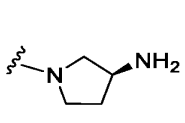
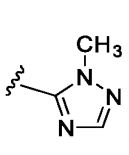
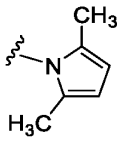
[0098] or a pharmaceutically acceptable salt thereof, wherein

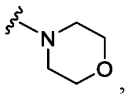
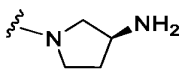
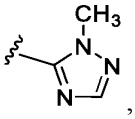
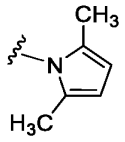
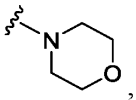
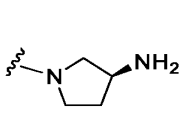
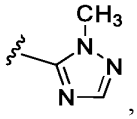
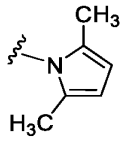
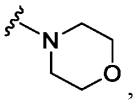
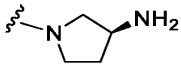
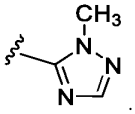
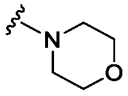
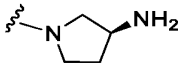
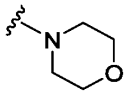
[0099] R3 is Cl, Br, methyl, trifluoromethyl or methoxy;

[0100] R4 is H, Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

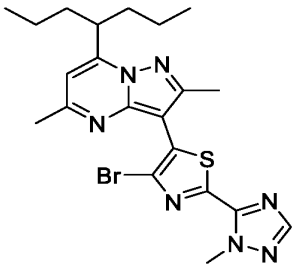
[0101] Ra and Rb are independently hydrogen, C1-C3 alkyl, H2NCH2CH2-, (CH3)3COC(O)NHCH2CH2-, or CH3CH2CH2NHCH2CH2.

[0102] For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be Cl, Br, methyl, trifluoromethyl, or methoxy. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be Cl, Br, methyl, or trifluoromethyl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be Cl, Br, or methyl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be Cl. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be Br. For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R3 may be methyl.

[0103] For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is Br, RaRbN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  . 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,  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is Br, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is Br, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is Br, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is

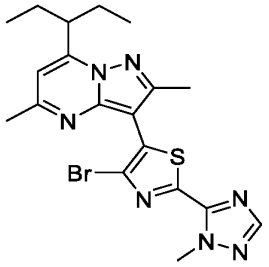
morpholin-4-yl,  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is  ,  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is  ,  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is  , or  . For a compound or pharmaceutically acceptable salt of Formula (I), (II), (III), and (IV), R4 is  .

[0104] Disclosed herein is 3-[4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]pyrimidine or a pharmaceutically acceptable salt thereof:



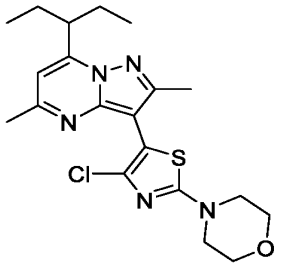
Compound 1

[0105] Disclosed herein is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine or a pharmaceutically acceptable salt thereof:



Compound 2

[0106] Disclosed herein is 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine (or alternatively 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine), a pharmaceutically acceptable salt thereof:



Compound 3.

[0107] In some embodiments, 4-(4-chloro-5-(2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-a]pyrimidin-3-yl)thiazol-2-yl)morpholine is referred to as Compound 3. In some embodiments, 3-(4-Chloro-2-(morpholin-4-yl)thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethylpyrazolo(1,5-a)pyrimidine is referred to as Compound 3.

[0108] In one aspect, the CRF1 antagonist or pharmaceutically acceptable salt thereof may be an astressin. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

Pharmaceutical Compositions

[0109] Disclosed herein are pharmaceutical compositions comprising a compound or pharmaceutically acceptable salt described herein. In certain embodiments, the composition comprises a steroid or a pharmaceutically acceptable salt thereof and a CRF_1 antagonist or pharmaceutically acceptable salt thereof as disclosed above. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is exogenous glucocorticoids (GC) or a pharmaceutically acceptable salt thereof.

Dosage Form

[0110] In some embodiments, the pharmaceutical compositions described herein are provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing

an amount of a compound or pharmaceutically acceptable salt described herein that is suitable for administration to an animal, preferably mammal, subject in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded.

[0111] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0112] In some embodiments, the pharmaceutical compositions described herein are formulated as oral dosage forms. Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules. In some embodiments, the pharmaceutical composition comprises one or more additional pharmaceutically acceptable excipients. See, e.g., Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005) for a list of pharmaceutically acceptable excipients.

Capsule

[0113] In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a hard gel capsule. In some embodiments, the pharmaceutical composition is formulated as a soft gel capsule.

[0114] In some embodiments, the capsule is formed using materials which include, but are not limited to, natural or synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, or any combinations thereof. In some embodiments, the capsule is formed using preservatives, coloring and opacifying agents, flavorings and sweeteners, sugars, gastroresistant substances, or any combinations thereof. In some embodiments, the capsule is coated. In some embodiments, the coating covering the capsule includes, but is not limited to, immediate release coatings, protective coatings, enteric or

delayed release coatings, sustained release coatings, barrier coatings, seal coatings, or combinations thereof. In some embodiments, a capsule herein is hard or soft. In some embodiments, the capsule is seamless. In some embodiments, the capsule is broken such that the particulates are sprinkled on soft foods and swallowed without chewing. In some embodiments, the shape and size of the capsule also vary. Examples of capsule shapes include, but are not limited to, round, oval, tubular, oblong, twist off, or a non-standard shape. The size of the capsule may vary according to the volume of the particulates. In some embodiments, the size of the capsule is adjusted based on the volume of the particulates and powders. Hard or soft gelatin capsules may be manufactured in accordance with conventional methods as a single body unit comprising the standard capsule shape. A single-body soft gelatin capsule typically may be provided, for example, in sizes from 3 to 22 minims (1 minims being equal to 0.0616 ml) and in shapes of oval, oblong or others. The gelatin capsule may also be manufactured in accordance with conventional methods, for example, as a two-piece hard gelatin capsule, sealed or unsealed, typically in standard shape and various standard sizes, conventionally designated as (000), (00), (0), (1), (2), (3), (4), and (5). The largest number corresponds to the smallest size. In some embodiments, the pharmaceutical composition described herein (e.g., capsule) is swallowed as a whole.

[0115] In some embodiments, the capsule comprises one or more pharmaceutically acceptable excipients. In some embodiments, the capsule is free of additional excipients.

[0116] In some embodiments, a capsule is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the capsule has a dose strength of up to 200 mg. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the capsule is immediately released in a dissolution medium using USP apparatus II.

Tablet

[0117] Poorly soluble drugs may be difficult to formulate using standard technologies such as high shear wet granulation. Optimum delivery of poorly soluble drugs may require complex technologies such as solid solutions amorphous dispersions (hot melt extrusion or spray drying), nano-formulations or lipid-based formulations. Hydrophobic drug substances may be considered poorly soluble according to USP criteria and may be known to be difficult to granulate with water and other excipients. This is likely due to most known excipients for immediate release formulations being water soluble or water-swellable. Making a tablet of a high dose drug substance that is poorly soluble may require a high concentration of the drug substance.

However, as the drug concentration is increased above a certain level, formation of granules may become more and more difficult. Furthermore, at a certain drug load, it may become impossible.

[0118] In some embodiments, the pharmaceutical composition is formulated as a tablet.

[0119] In some embodiments, the tablet is made by compression, molding, or extrusion, optionally with one or more pharmaceutically acceptable excipient. In some embodiments, compressed tablets are prepared by compressing a compound or pharmaceutically acceptable salt described herein in a free-flowing form, optionally mixed with pharmaceutically acceptable excipients. In some embodiments, molded tablets are made by molding a mixture of the powdered a compound or pharmaceutically acceptable salt described herein, moistened with an inert liquid diluent. In some embodiments, the tablet is prepared by hot-melt extrusion. In some embodiments, extruded tablets are made by forcing a mixture comprising a compound or pharmaceutically acceptable salt described herein, through an orifice or die under controlled conditions. In some embodiments, the tablet is coated or scored. In some embodiments, the tablet is formulated so as to provide slow or controlled release of a compound or pharmaceutically acceptable salt described herein. In some embodiments, a tablet is developed, manufactured and commercialized for a drug substance that is insoluble. In some embodiments, a drug substance is insoluble if solubility is less than 0.002 mg/mL in water. In some embodiments, the tablet has a dose strength of up to 200 mg. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus I. In some embodiments, drug substance in the tablet is immediately released in a dissolution medium using USP apparatus II.

[0120] In some embodiments, the tablet size is less than about 1000 mg, less than about 800 mg, less than about 600 mg, less than about 400 mg or less than about 200 mg. In some embodiments, the tablet has a dose strength of more than about 50 mg, more than about 100 mg, more than about 150 mg, more than about 200 mg, or more than about 250 mg. In some embodiments, the tablet size is less than about 1000 mg for a dose strength of more than about 50 mg. In some embodiments, the tablet size is less than 800 mg for a dose strength of more than about 100 mg. In some embodiments, the tablet size is less than 600 mg for a dose strength of more than about 150 mg. In some embodiment, the tablet size is less than 400 mg for a dose strength of more than about 200 mg. In some embodiments, the tablet size is less than 400 mg for a dose strength of 200 mg.

[0121] In some embodiments, more than about 20% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about

60% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 24 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 12 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 6 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 3 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 2 hours in conventional dissolution media. In some embodiments, more than about 20% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 40% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 50% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 60% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 70% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than about 80% of the tablet is dissolved in less than 60 minutes in conventional dissolution media. In some embodiments, more than 70% of the tablet is dissolved in 60 minutes in conventional dissolution media.

[0122] In some embodiments, the tablet is produced at a commercial scale.

[0123] In some embodiments, the tablet comprises one or more pharmaceutically acceptable excipients.

[0124] In some embodiments, the tablet is coated with a coating material, e.g., a sealant. In some embodiments, the coating material is water soluble. In some embodiments, the coating material comprises a polymer, plasticizer, a pigment, or any combination thereof. In some embodiments, the coating material is in the form of a film coating, e.g., a glossy film, a pH independent film coating, an aqueous film coating, a dry powder film coating (e.g., complete dry powder film coating), or any combination thereof. In some embodiments, the coating material is highly adhesive. In some embodiments, the coating material provides low level of water permeation. In some embodiments, the coating material provides oxygen barrier protection. In some embodiments, the coating material allows immediate disintegration for fast release of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the coating material is pigmented, clear, or white. In some embodiments, the coating is an enteric coating. Exemplary coating materials include, without limitation, polyvinylpyrrolidone,

polyvinyl alcohol, an acrylate-methacrylic acid copolymer, a methacrylate-methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, cellulose acetate trimellitate, sodium alginate, zein, and any combinations thereof.

Pharmaceutically Acceptable Excipients

[0125] In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient. In some embodiments, the composition is free of pharmaceutically acceptable excipients. The term "pharmaceutically acceptable excipient", as used herein, means one or more compatible solid or encapsulating substances, which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction, which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. In some embodiments, the pharmaceutically acceptable excipient is of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal, being treated.

[0126] Some examples of substances, which can serve as pharmaceutically acceptable excipients include:

- Amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, the amino acid is arginine. In some embodiments, the amino acid is L-arginine.
- Monosaccharides such as glucose (dextrose), arabinose, mannitol, fructose (levulose), and galactose.
- Cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose.
- Solid lubricants such as talc, stearic acid, magnesium stearate, and sodium stearyl fumarate.
- Polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol.
- Emulsifiers such as the polysorbates.
- Wetting agents such as sodium lauryl sulfate, Tween®, Span , alkyl sulphates, and alkyl ethoxylate sulphates.

- Diluents such as calcium carbonate, microcrystalline cellulose, calcium phosphate, starch, pregelatinized starch, sodium carbonate, mannitol, and lactose.
- Binders such as starches (corn starch and potato starch), gelatin, sucrose, hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMC).
- Disintegrants such as starch, and alginic acid.
- Super-disintegrants such as ac-di-sol, croscarmellose sodium, sodium starch glycolate and crospovidone.
- Glidants such as silicon dioxide.
- Coloring agents such as the FD&C dyes.
- Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors.
- Preservatives such as benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate, phenylmercuric nitrate, parabens, and sodium benzoate.
- Tonicity adjustors such as sodium chloride, potassium chloride, mannitol, and glycerin.
- Antioxidants such as sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA.
- pH adjuster such as NaOH, sodium carbonate, sodium acetate, HCl, and citric acid.
- Cryoprotectants such as sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran.
- Cationic surfactants such as cetrimide, benzalkonium chloride and cetylpyridinium chloride.
- Anion surfactants such as alkyl sulphates, alkyl ethoxylate sulphates, soaps, carboxylates, sulfates, and sulfonates.
- Non-ionic surfactants such as polyoxyethylene derivatives, polyoxypropylene derivatives, polyol derivatives, polyol esters, polyoxyethylene esters, poloxamers, glyol esters, glycerol esters, sorbitan derivatives, polyethylene glycol (PEG-40, PEG-50, PEG-55), and ethers of fatty alcohols.
- Organic materials such as carbohydrate and modified carbohydrates, lactose, a-lactose monohydrate, spray dried lactose and anhydrous lactose, starch and pre-gelatinized starch, sucrose, manitol, sorbitol, cellulose, powdered cellulose and microcrystalline cellulose.

- Inorganic materials such as calcium phosphates (anhydrous dibasic calcium phosphate, dibasic calcium phosphate and tribasic calcium phosphate).
- Co-processed diluents.
- Surfactants such as sodium lauryl sulfate.
- Compression aids.
- Anti-tacking agents such as silicon dioxide and talc

Amounts

[0127] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 500 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 400 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 300 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 200 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 100 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 90 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 80 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 70 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 60 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 50 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 40 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 30 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 20 mg

of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 1 mg and about 10 mg of a compound or pharmaceutically acceptable salt described herein.

[0128] In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 500 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 400 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 300 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 200 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 100 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 90 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 80 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 70 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 60 mg of a compound or pharmaceutically acceptable salt described herein f. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 50 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 40 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 30 mg of a compound or pharmaceutically acceptable salt described herein. In some embodiments, the pharmaceutical composition, in the form of a tablet or capsule, comprises between about 10 mg and about 20 mg of a compound or pharmaceutically acceptable salt described herein.

Particle size

[0129] In some embodiments, the pharmaceutical composition, in the form of a tablet or a capsule, comprises a compound or pharmaceutically acceptable salt described herein, in the form

of microparticles. In some embodiments, the microparticles have an average size from about 1 μm to about 100 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 50 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 30 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 20 μm. In some embodiments, the microparticles have an average size from about 5 μm to about 15 μm. In some embodiments, the microparticles have an average size from about 1 μm to about 10 μm. In some embodiments, the microparticles have an average size from about 3 μm to about 10 μm. In some embodiments, the microparticles have an average size from about 4 μm to about 9 μm.

Methods of Treatment

[0130] Disclosed herein are methods of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering a compound or pharmaceutically acceptable salt described herein. In some embodiments, the methods described herein result in the reduction of a level of a hormone. Such hormones include deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, 17-OHP, dehydroepiandrosterone, androstenediol, A4, testosterone, dihydrotestosterone, estrone, estradiol, estriol, and ACTH. In some embodiments, the methods described herein result in the reduction of 17-OHP levels. In some embodiments, the methods described herein result in the reduction of A4 levels. In some embodiments, the methods described herein result in the reduction of ACTH levels, also known as corticotropin.

[0131] Further, in some embodiments, the methods described herein result in the maintenance of the reduction of 17-OHP, A4, and/or ACTH levels. In some embodiments, the reductions of 17-OHP, A4, and/or ACTH levels may last for at least 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 2 years, 5 years, 10 years, 15 years, 20 years, 25 years, 30 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years, or 100 years.

[0132] Moreover, the present disclosure provides different patient subtype regimens for treating Congenital Adrenal Hyperplasia (CAH) patients. In one aspect, the present disclosure provides a method of treating Congenital Adrenal Hyperplasia (CAH), comprising administering

an effective amount of a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof to a subject, i.e., a CAH patient/individual, over a 24 hour period, which the effective amount of the steroid is dependent on the levels of steroid hormones, such as ACTH, A4, 17-OHP, or any combinations thereof, of the subject measured at the time of beginning the treatment of CAH, typically in the am. Prior to implementing the method of treatment disclosed herein, a CAH patient may be evaluated to determine the patient's plasma steroid hormone levels.

[0133] Generally, a normal range, a normal laboratory reference range, or a reference range of ACTH level or A4 level in a subject may be broad and dependent on many different factors. For example, ACTH, 17-OHP or A4 is secreted in bursts with a daily rhythm in a subject. Plasma samples collected at 8 am in the morning may show different range of ACTH or A4 levels in a subject compared to plasma samples collected at 2 pm, 4 pm, or midnight during the day. Further, the normal range of ACTH or A4 levels are dependent on a factor such as laboratory setting. Laboratory setting may comprise different types of assays for detecting ACTH or A4 levels, equipment utilized in the laboratory, personnel in the laboratory performing the assays, and different batches of reagents used during the assays. Different ages of a subject may provide different normal ranges of ACTH or A4 levels as well. Moreover, a normal range of ACTH level or A4 level in a subject may be dependent on the sex of the subject. For example, not meant to be limiting, a male subject's normal range of ACTH level may be from 7 to 63.3 pg/mL, as assessed in the am, typically before 10 am, and A4 level, also assessed in the am, typically before 10 am, may be from 50 to 220 ng/dL for males aged 18 to 30 years, from 40 to 190 ng/dL for males aged 31 to 50 years and from 50 to 220 ng/dL for males aged 51 to 60 years. Additionally, a normal range of ACTH level or A4 level in a female subject may be dependent on the female subject's menopausal stage. For example, not meant to be limiting, a pre-menopausal female subject's normal range of ACTH level may be from 7 to 63 pg/mL, as assessed in the am, typically before 10 am, and A4 level may be from 51 to 213 ng/dL for women in the mid-follicular stage, from 73 to 230 ng/dL for women in the surge stage, from 73 to 184 for women in the mid luteal stage. A post-menopausal female subject's normal range of ACTH level may be from 7 to 63.3 pg/mL and A4 level may be from 20 to 75 ng/dL. Normal ranges for PM assessments of ACTH and A4 have not been established.

[0134] In some embodiments, when a subject has levels that are less than two (2) times an upper limit of the normal ranges or the normal laboratory reference ranges of ACTH and A4 level respectively, a percentage of the total daily GC dose, typically done in 5 mg hydrocortisone equivalents, of the effective amount of the steroid or a pharmaceutically acceptable salt thereof is reduced compared to a dose of the effective amount of the steroid or a pharmaceutically

acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has a level that is less than 2 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is less than 1.75 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is less than 1.5 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is less than 1.25 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is less than 1.0 times the upper limit of the normal range of ACTH or A4 level.

[0135] In certain embodiments, as long as the levels of both the ACTH and A4 are less than 2 times an upper limit of the normal reference ranges of ACTH and A4 respectively, the dosage of the steroid or a pharmaceutically acceptable salt thereof is reduced. For example, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1.75 times the upper limit of the normal range of ACTH and A4 level is less than 1.25 the upper limit of the normal range of A4. Further, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1.25 times the upper limit of the normal range of ACTH and A4 level is less than 1.5 the upper limit of the normal range of A4. Moreover, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1.5 times the upper limit of the normal range of ACTH and A4 level is less than 1.5 the upper limit of the normal range of A4. Additionally, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1.25 times the upper limit of the normal range of ACTH and A4 level is less than 1.25 the upper limit of the normal range of A4.The regimen of treating with reduced amount of the steroid or a pharmaceutically acceptable salt thereof compared to the amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof may be utilized. The reduction of GC daily does may be done in a 5 mg hydrocortisone equivalents, 4 mg hydrocortisone equivalents, 3 mg hydrocortisone equivalents, 2 mg hydrocortisone equivalents, 1 mg hydrocortisone equivalents, or 0.5 mg hydrocortisone equivalents.

[0136] In some embodiments, when a subject has levels that are less than two (2) times an upper limit of the normal ranges or the normal laboratory reference ranges of ACTH and 17-OHP level respectively, a percentage of the total daily GC dose, typically done in 5 mg hydrocortisone equivalents, of the effective amount of the steroid or a pharmaceutically acceptable salt thereof is reduced compared to a dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e.,

a compound disclosed herein) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has a level that is less than 2 times the upper limit of the normal range of ACTH or 17-OHP level. In some embodiments, the subject has a level that is less than 1.75 times the upper limit of the normal range of ACTH or 17-OHP level. In some embodiments, the subject has a level that is less than 1.5 times the upper limit of the normal range of ACTH or 17-OHP level. In some embodiments, the subject has a level that is less than 1.25 times the upper limit of the normal range of ACTH or 17-OHP level. In some embodiments, the subject has a level that is less than 1.0 times the upper limit of the normal range of ACTH or 17-OHP level. As long as the levels of both the ACTH and 17-OHP are less than 2 times an upper limit of the normal reference ranges of ACTH and 17-OHP respectively, the dosage of the steroid or a pharmaceutically acceptable salt thereof is reduced. For example, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1.5 times the upper limit of the normal range of ACTH and 17-OHP level is less than 1.75 the upper limit of the normal range of 17-OHP. Further, a CAH patient's biological sample may be measured to show that the patient's ACTH level is less than 1 times the upper limit of the normal range of ACTH and 17-OHP level is less than 1.25 the upper limit of the normal range of 17-OHP. The regimen of treating with reduced amount of the steroid or a pharmaceutically acceptable salt thereof compared to the amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof may be utilized.

[0137] In some embodiments, when a subject has levels that are less than two (2) times an upper limit of the normal ranges or the normal laboratory reference ranges of A4 and 17-OHP level respectively, a percentage of the total daily GC dose, typically done in 5 mg hydrocortisone equivalents, of the effective amount of the steroid or a pharmaceutically acceptable salt thereof is reduced compared to a dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has a level that is less than 2 times the upper limit of the normal range of A4 or 17-OHP level. In some embodiments, the subject has a level that is less than 1.75 times the upper limit of the normal range of A4 or 17-OHP level. In some embodiments, the subject has a level that is less than 1.5 times the upper limit of the normal range of A4 or 17-OHP level. In some embodiments, the subject has a level that is less than 1.25 times the upper limit of the normal range of A4 or 17-OHP level. In some embodiments, the subject has a level that is less than 1.0 times the upper limit of the normal range of A4 or 17-OHP level. As long as the levels of both the A4 and 17-OHP are less than 2 times an upper limit of the normal reference ranges of

A4 and 17-OHP respectively, the dosage of the steroid or a pharmaceutically acceptable salt thereof is reduced. For example, a CAH patient's biological sample may be measured to show that the patient's A4 level is less than 1 times the upper limit of the normal range of A4 and 17-OHP level is less than 1.75 the upper limit of the normal range of 17-OHP. Further, a CAH patient's biological sample may be measured to show that the patient's A4 level is less than 1.5 times the upper limit of the normal range of A4 and 17-OHP level is less than 1.25 the upper limit of the normal range of 17-OHP. The regimen of treating with reduced amount of the steroid or a pharmaceutically acceptable salt thereof compared to the amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof may be utilized.

[0138] When a CRF1 antagonist is not administered, treatment of CAH patients needs to replace the cortisol deficiency and normalize the excess androgen production, which is a sequalae of the enzymatic deficiency in CAH, by administering exogenous glucocorticoids (GC) at a dose that is usually well above the normal physiologic does used for cortisol replacement in patients with other diseases, such as Addison's disease. Reduced levels of exposure to steroids, form supraphysiologic to physiologic levels, may be beneficial to CAH patients. In some embodiments, a dose of about 10 mg to about 80 mg GC is administered to a CAH patient when a CRF1 antagonist is not administered. In some embodiments, the dose of GC is administered to CAH patients one time, two times, three times, or four times daily.

[0139] For example, not meant to be limiting, a dose of about 80mg GC could be administered to a CAH patient when a CRF1 antagonist is not administered. If this CAH patient's ACTH level and A4 level are less than 2, 1.5, or 1.25 times the upper limit of the normal range of ACTH level and A4 levels respectively after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80mg GC may be reduced in a 5 mg hydrocortisone equivalent increment when administered together with the CRF1 antagonist (i.e., a compound disclosed herein). In some embodiments, a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof in a dose of about 10 mg to about 200 mg total daily dose is administered to the subject. The CAH patient may be receiving a dose of 75 mg GC during the treatment regimen when the compound is administered together. After a certain period, when the CAH patient's ACTH level and A4 levels remain less than 2, 1.5, or 1.25 times the upper limit of the normal range of the ACTH and A4 levels respectively, the dose of 75 mg GC may be further reduced in a 5 mg increment to 70 mg when administered with the CRF1 antagonist. The dose of the GC may be continuously reduced in a 5 mg increment hydrocortisone equivalent when administered together with the CRF1 antagonist, over a 24 hour

period, until the subject's ACTH or A4 level is not less than 2, 1.5, or 1.25 times the upper limit of the normal range of ACTH or A4 level.

[0140] Moreover, if this CAH patient's ACTH level is less than 1.75 times the upper limit of the normal range of ACTH level and A4 level is less than 1.5 times the upper limit of the normal range of A4 level after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80mg GC may be reduced in a 5 mg increment when administered together the CRF1 antagonist (i.e., a compound disclosed herein). If this CAH patient's ACTH level is less than 1.5 times the upper limit of the normal range of ACTH level and A4 level is less than 1.75 times the upper limit of the normal range of A4 level after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80mg GC may be reduced in a 5 mg increment when administered together the CRF1 antagonist (i.e., a compound disclosed herein). If this CAH patient's ACTH level is less than 1.25 times the upper limit of the normal range of ACTH level and A4 level is less than 1.25 times the upper limit of the normal range of A4 level after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80mg GC may be reduced in a 5 mg increment when administered together the CRF1 antagonist (i.e., a compound disclosed herein). In some embodiments, if this CAH patient's ACTH level is less than 1.0 times the upper limit of the normal range of ACTH level and A4 level is less than 1.0 times the upper limit of the normal range of A4 level after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80mg GC may be reduced in a 5 mg increment when administered together with the CRF1 antagonist (i.e., a compound disclosed herein).

[0141] In some embodiments, the subject will be treated for a period of about 1 week to about 40 weeks. In some embodiments, the subject will be treated for a period of about 2 weeks to about 39 weeks. In some embodiments, the subject will be treated for a period of about 3 weeks to about 38 weeks. In some embodiments, the subject will be treated for a period of about 4 weeks to about 36 weeks. In some embodiments, if a subject has been treated for a period of time described herein and has levels of A4 and ACTH less than the lower limit of the normal laboratory reference range, the subject may continue with steroid reduction until the subject maintain hormone levels consistently within the normal range of A4 and ACTH.

[0142] Further, in some embodiments, when a subject has a level that is more than an upper limit of the normal range or the normal laboratory reference range of ACTH or A4 level, the total daily dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof is not reduced compared to a dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof. In some

embodiments, the subject has a level that is more than 2 times the upper limit of the normal range of ACTH or A4 level. Some subjects may further be categorized as having severe control issues when the subjects have more than 4 times an upper limit of the normal range of both ACTH and A4 levels. Moreover, some subjects may be further categorized as having moderate control issues when the subjects have more than 2 times the upper limit of normal range of the ACTH level but less than 4 times the upper limit of normal range of the A4 level. In some embodiments, the subject has a level that is more than 1.75 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is more than 1.5 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is more than 1.25 times the upper limit of the normal range of ACTH or A4 level. In some embodiments, the subject has a level that is more than 1.0 times the upper limit of the normal range of ACTH or A4 level.

[0143] Additionally, in some embodiments, when a subject has an ACTH level that is more than an upper limit of the normal range or the normal laboratory reference range of ACTH level and an A4 level that is more than an upper limit of the normal range or the normal laboratory reference range of A4, the total daily dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof is not reduced compared to a dose of the effective amount of the steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient without receiving a CRF1 antagonist (i.e., a compound disclosed herein) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has an ACTH level that is more than 1.75 times the upper limit of the normal range of ACTH and an A4 level that is more than 1.5 times the upper limit of the normal range of A4. In some embodiments, the subject has an ACTH level that is more than 1.5 times the upper limit of the normal range of ACTH and an A4 level that is more than 1.25 times the upper limit of the normal range of A4. In some embodiments, the subject has an ACTH level that is more than 1.25 times the upper limit of the normal range of ACTH and an A4 level that is more than 1 times the upper limit of the normal range of A4. In some embodiments, the subject has an ACTH level that is more than 1 times the upper limit of the normal range of ACTH and an A4 level that is more than 1.25 times the upper limit of the normal range of A4. In some embodiments, the subject has an ACTH level that is more than 1.25 times the upper limit of the normal range of ACTH and an A4 level that is more than 1.5 times the upper limit of the normal range of A4. In some embodiments, the subject has an ACTH level that is more than 1.5 times the upper limit of the normal range of ACTH and an A4 level that is more than 1.75 times the upper limit of the normal range of A4.

[0144] In some embodiments, a dose of about 10 mg to about 80 mg GC is administered to a CAH patient when a CRF1 antagonist is not administered. In some embodiments, the dose of

GC is administered to CAH daily one time, two times, three times, or four times. In some embodiments, a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof in a dose of about 10 mg to about 200 mg total daily dose is administered to the subject. For example, not meant to be limiting, a dose of about 80 mg GC administered to a CAH patient when a CRF1 antagonist is not administered. If this CAH patient's ACTH level or A4 level is more than the upper limit of the normal range of ACTH level or A4 level after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80 mg GC may be maintained when administered together the CRF1 antagonist (i.e., a compound disclosed herein). Further, if this CAH patient's ACTH level and A4 levels are more than the upper limit of the normal range of ACTH level and A4 level respectively after controlled by factors such as age, sex, menopausal status, laboratory setting, the dose of 80 mg GC may be maintained when administered together the CRF1 antagonist (i.e., a compound disclosed herein).

[0145] During the treatment of administering the maintained dose of GC together with the CRF1 antagonist, the CAH patient's ACTH and A4 levels are monitored. In some embodiments, as soon as the CAH patient's ACTH and A4 level become less than 2 times the upper limit of the normal range of the ACTH and A4 level respectively, the dose of GC may be reduced in a 5 mg hydrocortisone equivalent increment to the CAH patient when administered together with the CRF1 antagonist. In some embodiments, as soon as the CAH patient's ACTH and A4 levels become less than 1.75 times the upper limit of the normal range of the ACTH and A4 level respectively, the dose of GC may be reduced in a 5 mg hydrocortisone equivalent increment to the CAH patient when administered together with the CRF1 antagonist. In some embodiments, as soon as the CAH patient's ACTH and A4 levels become less than 1.5 times the upper limit of the normal range of the ACTH and A4 level respectively, the dose of GC may be reduced in a 5 mg hydrocortisone equivalent increment to the CAH patient when administered together with the CRF1 antagonist. In some embodiments, as soon as the CAH patient's ACTH and A4 levels become less than 1.25 times the upper limit of the normal range of the ACTH and A4 levels respectively, the dose of GC may be reduced in a 5 mg hydrocortisone equivalent increment to the CAH patient when administered together with the CRF1 antagonist. In some embodiments, as soon as the CAH patient's ACTH and A4 levels become less than 1.0 times the upper limit of the normal range of the ACTH and A4 levels respectively, the dose of GC may be reduced in a 5 mg hydrocortisone equivalent increment to the CAH patient when administered together with the CRF1 antagonist. Moreover, the dose of the GC may be continuously reduced in a 5 mg increment when administered together with the CRF1 antagonist until the subject's ACTH and A4 levels are not less than 2, 1.5, or 1.25 times the upper limit of the normal range of ACTH and A4 levels respectively.

[0146] In some embodiments, the subject will be treated for a period of about 1 week to about 40 weeks. In some embodiments, the subject will be treated for a period of about 2 weeks to about 39 weeks. In some embodiments, the subject will be treated for a period of about 3 weeks to about 38 weeks. In some embodiments, the subject will be treated for a period of about 4 weeks to about 36 weeks. In some embodiments, after the subject has been treated for a period of time described herein, the subject may be reassessed to determine whether a different patient subtype regimen may be applicable.

[0147] In some embodiments, the dose of steroid or a pharmaceutically acceptable salt thereof is in a dose of about 10 mg to about 80 mg of hydrocortisone equivalents. In some embodiments, the steroid is a glucocorticoid or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is tested in the morning to determine morning levels of A4 and ACTH.

[0148] With specificity provided from a particular laboratory setting, in some embodiments, two times the upper limit of the normal laboratory reference range of A4 for a male subject is more than about 440 ng/dl, more than about 430 ng/dl, more than about 420 ng/dl, more than about 410 ng/dl, more than about 400 ng/dl, more than about 390 ng/dl, more than about 380 ng/dl, more than about 370 ng/dl. In some embodiments, the normal laboratory reference range of A4 for a male subject is from about 40 ng/dl to about 190 ng/dl. In some embodiments, the normal laboratory reference range of A4 for a male subject is from about 50 ng/dl to about 220 ng/dl.

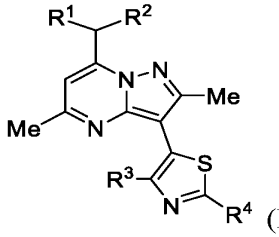
[0149] In some embodiments, two times the upper limit of the normal laboratory reference range of A4 for a female subject is more than about 560 ng/dl, more than about 550 ng/dl, more than about 540 ng/dl, more than about 530 ng/dl, more than about 520 ng/dl, more than about 510 ng/dl, 500 ng/dl, more than about 490 ng/dl, more than about 480 ng/dl, more than about 470 ng/dl, more than about 460 ng/dl, more than about 450 ng/dl, more than about 430 ng/dl, more than about 420 ng/dl, more than about 410 ng/dl, 400 ng/dl, more than about 390 ng/dl, more than about 380 ng/dl, more than about 370 ng/dl, more than about 360 ng/dl, more than about 350 ng/dl, or more than about 340 ng/dl. In some embodiments, the normal laboratory reference range of A4 for a female subject is from about 51 ng/dl to about 213 ng/dl. In some embodiments, the normal laboratory reference range of A4 for a female subject is from about 73 ng/dl to about 230 ng/dl. In some embodiments, the normal laboratory reference range of A4 for a female subject is from about 73 ng/dl to about 184 ng/dl.

[0150] In some embodiments, two time the upper limit of the normal laboratory reference of ACTH is more than about 110 pg/dl, more than about 120 pg/dl, more than about 130 pg/dl,

more than about 140 pg/dl, or more than about 150 pg/dl. In some embodiments, the normal laboratory reference range of ACTH is from about 7 pg/dl to about 70 pg/dl.

[0151] In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003.

[0152] In some embodiments, the CRF_1 antagonist is a compound of Formula (I):

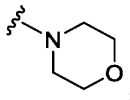
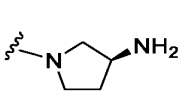
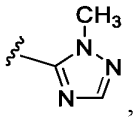
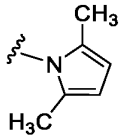


(I),

or a pharmaceutically acceptable salt thereof, wherein:

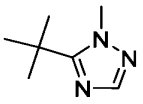
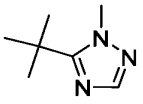
R^1 and R^2 are independently ethyl or *n*-propyl;

R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

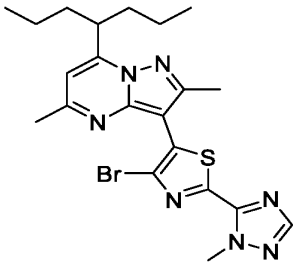
R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

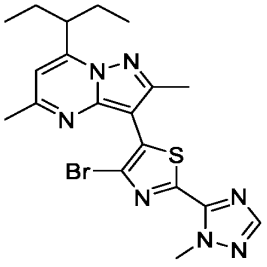
[0153] In some embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl.

[0154] In some embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is morpholin-4-yl or  . In some embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

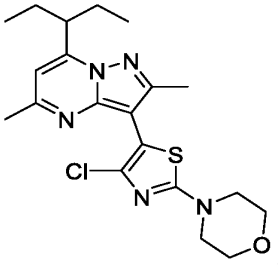
[0155] In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

[0156] In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

[0157] In some embodiments, the compound is


, or a pharmaceutically acceptable salt thereof.

[0158] In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg to about 200 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

[0159] In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 40 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 30 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 20 mg

total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 15 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 10 mg total daily dose to the subject. In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 5 mg total daily dose to the subject.

[0160] In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt is in the form of microparticles. In some embodiments, the average size of the microparticles is between about 1 μm to about 20 μm. In some embodiments, the average size of the microparticles is between about 5 μm to about 15 μm. In some embodiments, the average size of the microparticles is less than about 10 μ.

[0161] In some embodiments, the CRF1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition. In some embodiments, the steroid or a pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

[0162] In some embodiments, the pharmaceutical composition is in the form of a capsule or a tablet. In some embodiments, the capsule is a hard gelatin capsule. In some embodiments, the capsule is a soft gelatin capsule. In some embodiments, the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

[0163] In some embodiments, the pharmaceutical composition is free of additional excipients. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0164] In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 1 to about 8 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 to about 7 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 to about 6 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 3 to about 5 hours in a subject.

[0165] In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 8 hours in a subject. In some

embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 7 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 6 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 5 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 4 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 3 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 2 hours in a subject. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is formulated as a capsule or a tablet as to provide a Tmax of about 1 hour in a subject.

[0166] In some embodiments, the methods described herein include administration of the pharmaceutical composition comprising CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof once a month, twice a month, three times a month, once a week, twice a week, three times a week, once every two days, once a day, twice a day, three times a day, or four times a day. In some embodiments, the methods described herein administer CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof once a day. In some embodiments, the methods described herein administer CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof twice a day.

[0167] In some embodiments, the methods described herein include administration of about 1 mg to about 2000 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, per day. In some embodiments, CRF1 antagonist or pharmaceutically acceptable salt is administered at a dose between about 50 mg/day and about 1600 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1500 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1400 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1300 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1200 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1100 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 1000 mg/day. In some embodiments, Compound 1 is administered at a dose between about 50 mg/day and about 900 mg/day. In some embodiments, Compound 1 is

administered at a dose between about 50 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 60 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 70 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 80 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 90 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 800 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 700 mg/day. In some embodiments, Compound 1 is administered at a dose between about 100 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 150 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 600 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 500 mg/day. In some embodiments, Compound 1 is administered at a dose between 200 mg/day and about 400 mg/day.

[0168] In some embodiments, Compound 1 is administered at a dose of about 500 mg/day. In some embodiments, Compound 1 is administered at a dose of about 400 mg/day. In some embodiments, Compound 1 is administered at a dose of about 300 mg/day. In some embodiments, Compound 1 is administered at a dose of about 200 mg/day. In some embodiments, Compound 1 is administered at a dose of about 100 mg/day.

[0169] In some embodiments, about 100 mg to about 1600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1200 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 1000 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 800 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 800 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is

administered per day. In some embodiments, about 200 mg to about 600 mg of CRF1 antagonist or pharmaceutically acceptable salt is administered per day. In some embodiments, about 300 mg to about 600 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 100 mg to about 400 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 200 mg to about 400 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, about 300 mg to about 400 mg of CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered each day.

[0170] In some embodiments, less than about 2000 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1800 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1600 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1400 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1200 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 1000 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 800 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 600 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 500 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 400 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 300 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day. In some embodiments, less than about 200 mg CRF1 antagonist or pharmaceutically acceptable salt, or a pharmaceutically acceptable salt or solvate thereof, is administered per day.

[0171] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein wherein the subject is in the fed state. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein wherein the subject is in the fasted state.

[0172] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at bedtime.

[0173] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 4 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 3 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 2 hours before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 1 hour before sleep. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein less than about 30 mins before sleep.

[0174] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein in the evening.

[0175] In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 11 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 10 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 9 pm at night. In some embodiments, the methods described herein include administration of the pharmaceutical compositions described herein at about 8 pm at night.

[0176] In some embodiments, the steroid or pharmaceutically acceptable salt thereof is a glucocorticoid or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid or a pharmaceutically acceptable salt there is prednisone, cortisone, prednisolone, triamcinolone, methylprednisolone, betamethasone, dexamethasone, hydrocortisone or a pharmaceutically acceptable salt thereof.

[0177] In some embodiments, the levels of A4 and ACTH in the subject are determined from a biological sample from the subject. In some embodiments, the biological sample is selected from the group of blood, blood fractions, plasma, serum, urine, other types of bodily secretions, and saliva. In some embodiments, the biological sample is obtained non-invasively.

[0178] In some embodiments, the subject is a pediatric patient. In some embodiments, the subject is from about 0 years old to about 18 years old. In some embodiments, the subject is an adult patient.

[0179] In some embodiments, the steroid and the CRF1 antagonist are administered concurrently. In some embodiments, the steroid and the CRF1 antagonist are administered in one pharmaceutical composition. In some embodiments, the steroid and the CRF1 antagonist are administered concurrently in separate pharmaceutical compositions. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially.

[0180] In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 24 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 8 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 2 hours. In some embodiments, the steroid and the CRF1 antagonist are administered sequentially within 10 minutes.

[0181] In some embodiments, CAH is classic CAH. In some embodiments, CAH is non-classic CAH.

[0182] In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the glucocorticoid is hydrocortisone.

[0183] In some embodiments, the glucocorticoid is hydrocortisone and the dose administered is less than the recommended dose of 15-25 mg/day.

[0184] In some embodiments, the glucocorticoid is prednisone and the dose administered is less than the recommended dose of 5-7.5 mg/day.

[0185] In some embodiments, the glucocorticoid is prednisolone and the dose administered is less than the recommended dose of 4-6 mg/day.

[0186] In some embodiments, the glucocorticoid is dexamethasone and the dose administered is less than the recommended dose of 0.25-0.5 mg/day.

EXAMPLES

[0187] The following examples further illustrate the invention but should not be construed as in any way limiting its scope. In particular, the processing conditions are merely exemplary and can be readily varied by one of ordinary skill in the art.

[0188] All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed.

Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

Example 1 – Identifying discrete subgroups of patients with CAH based on A4 and ACTH levels in a subject who has CAH

[0189] Study Compound 3, a Phase 2, open-label, first-in-CAH-patients, proof-of-concept, dose ranging study, evaluated the safety and efficacy of repeated doses of SPR001 in adults with classic CAH. The population (n=24; with 2 subjects completing 2 cohorts) consisted of subjects with classic CAH that is not adequately controlled despite a stable glucocorticoid regimen based on the assessment of a single hormone at study screening, 17-OHP > 800 ng/dl, which is 4 times the upper limit of a normal reference range of 17-OHP level. 17-OHP was chosen as the hormone as an inclusion criterion, as at the time, it represented the state-of-art in CAH for assessment of disease severity and adequacy of glucocorticoid therapy. The study comprised 3 cohorts, Cohort A was a 6-week intra-subject dose escalation treatment period with three 2-week treatment periods of 200 mg glucocorticoid (QD) (only daily), 600 mg QD and 1000 mg QD without washout between treatment periods. Cohorts B and C consisted of 2-week treatment periods of either 100 bis in die (BID) (twice daily) (Cohort C) or 200 mg BID (Cohort B). At baseline, the following hormones were assessed, 17-OHP, ACTH and A4. The same hormones were assessed at the end of each 2-week treatment period.

[0190] The inclusion criterion of an elevated 17-OHP (>800 ng/dL) was expected, based on the current state-of-art, to enroll subjects with elevated ACTH, a precursor to 17-OHP, and elevated A4, a downstream androgen of 17-OHP. An elevated 17-OHP corresponded to both elevated and non-elevated pre (ACTH) and post (A4) stream hormones. This is evidenced in Table 1. All cohorts met the criteria of elevated 17-OHP as evidenced in the geometric means. Subjects in Cohort B, while having elevated 17-OHP, did not have elevated ACTH or elevated A4. Cohorts A and C had all 3 hormones elevated corresponding to the state-of-the-art.

Table 1 – Cohorts assessed in a Phase 2, open-label, first-in-CAH-patients, proof-of-concept, dose ranging study

	Cohort A Compound 3 200/600/1000 QD (N=10)	**Cohort B Compound 3 200 BID (N=8)**	**Cohort C Compound 3 100 BID (N=7)**
Screening 17-OHP, ng/dL			
Geometric Mean (CV%)	3887.3 (125.6)	3157.8 (109.1)	6106.8 (113.6)
Baseline (8am) 17-OHP, ng/dL			
Geometric Mean (CV%)	7362.0 (95.2)	1954.2 (344.2)	6753.4 (96.0)
Baseline (8 am)ACTH, pg/mL			

Geometric Mean (CV%)	306.72 (97.1)	27.17 (190.6)	292.45 (100.9)
Baseline (8am) A4, ng/dL			
Geometric Mean (CV%)	286.9 (168.1)	93.0 (194.6)	242.2 (121.8)

[0191] A clustering approach, supported and guided by clinical input, was used to define subgroups based on baseline hormone control of A4 and ACTH. The inclusion of 17-OHP as an input occluded the identification of clear subgroups which was non-obvious.

[0192] Three subgroups of patients were identified (see FIG.1):

- Subgroup One: Subjects with A4 and ACTH levels generally lower than two-fold the upper limit of normal for each laboratory assessment respectively.
- Subgroup Two: Subjects with A4 and ACTH generally higher than two-fold the upper limit of normal for each laboratory assessment respectively.
- Subgroup Three: Subjects with either A4 or ACTH above two fold and the other below two-fold the upper limit of normal for each laboratory assessment respectively.
- Subgroups 2 and 3 can be combined into a single subgroup.

[0193] By classifying the patients into subgroup types based on A4 and ACTH, it provides an alternative method to assessing diseases severity of subjects based on 17-OHP and A4. In addition, these subgroups provide a basis for different, yet sequential, methods of treatment.

Example 2 –Phase 2 Clinical Studies

[0194] A clinical study is conducted involving up to 52 weeks treatment of Compound 3 with concurrent daily glucocorticoid therapy for the treatment of adults with classic CAH. After screening using A4 and ACTH level criteria, eligible patients are enrolled into up to 12 weeks of placebo-controlled treatment followed by 40 weeks of open label treatment and a 4-week washout/safety follow-up period.

[0195] The population are composed of subjects from subgroup 2, approximately n=18 per treatment group and a range of doses between 50 mg to 200 mg and placebo. Each subject receives Compound 3 or placebo and a glucocorticoid daily for up to 12 weeks in a double-blind matter. Following the placebo-controlled period, all subjects receive open label compound 3 as various doses and a glucocorticoid will be administered as an oral daily dose as in the double-blind period. Patients self-administer Compound 3 for up to 52 weeks. The maximum treatment period for placebo is 12 weeks.

[0196] Study Design

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 2

- Interventional Study Model: double-blind, placebo controlled (12 weeks), open label (up to 40 weeks)
- Allocation: Equal Randomization
- Enrollment: Up to approximately 72

Outcome Measures

Primary Outcome Measures:

1. Assess reduction in key hormones such as ACTH, A4 and 17-OHP.

Secondary Outcome Measures:

2. Assess normalization proportions for key hormones such as ACTH, A4 and 17-OHP.

Eligibility

- Minimum Age: 16 Years
- Maximum Age: 65 Years
- Sex: All
- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated A4 and ACTH more than two times the upper limit of normal laboratory reference range at screening and baseline
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

[0197] The disclosed compound 3 is an inhibitor of the CYP3A4 pathway and dexamethasone (DEX) is primarily metabolized through the CYP3A4 pathway. As part of the study, pre and pose concentrations of DEX and cortisol were measured. In some embodiments, the biomarker reduction analysis comprises all subjects. In some embodiments, the biomarker reduction analysis does not comprise DEX-treated subjects.

[0198] As shown in FIGS. 2A and 2B, time matched changes among different treatment groups of ACTH level measured from 10 pm the day before to 8am the next day are illustrated in

non-dexamethasone subjects. A pooled baseline (dotted) and 2 lines (solid) representing two dose groups (doses = 200 mg and doses > 200 mg) using the percentage change from dose group baseline presented as percentage change from the pooled baseline. The figures are divided by disease control group, poor disease control with highly elevated ACTH and A4 and the good disease control group with ACTH and A4 that is near normal or below normal ranges. Each group has elevated 17-OHP.

[0199] According to FIG. 2A, in the poor disease group the geometric means post 4 am are highly elevated reaching values greater than 400 pg/mL or greater than 6 x upper limit of normal (ULN)(63.3 pg/mL). Treatment with compound 3 reduced the magnitude of the increase in ACTH post 3 am demonstrating an improvement in the serial hormone profile. According to FIG. 2B, in the good disease control group, the baseline serial profile was below the ULN throughout the evaluated time period. Treatment with compound 3 generally maintained the serial profile below the ULN. The observed changes are likely representative of intra-subject daily variation.

[0200] As shown in FIGS. 3A and 3B, the time matched changes among different treatment groups of 17-OHP level measured from 10 pm the day before to 8am the next day are illustrated in non-dexamethasone subjects . A pooled baseline (dotted) and 2 lines (solid) representing two dose groups (doses = 200 mg and doses > 200 mg) using the percentage change from dose group baseline presented as percentage change from the pooled baseline. The figures are divided by disease control group, poor disease control with highly elevated ACTH and A4 and the good disease control group with ACTH and A4 that is near normal or below normal ranges. In both groups, 17-OHP is elevated above its target (1200 ng/dL). The Y-axis is different with the poor disease control group exceeding 8000 ng/dL in FIG. 3A and the good disease group was near an upper bound of approximately 3000 ng/dL in FIG. 3B. In both groups, treatment with compound 3 reduced the magnitude of the increase in 17-OHP post 3 am demonstrating an improvement in the serial hormone profile.

[0201] As shown in FIGS. 4A and 4B, the time matched changes among different treatment groups of A4 level measured from 6 am to 8 am the same day in non-dexamethasone subjects. A pooled baseline (dotted) and 2 lines (solid) representing two dose groups (doses = 200 mg and doses > 200 mg) using the percentage change from dose group baseline presented as percentage change from the pooled baseline. The figures are divided by disease control group, poor disease control with highly elevated ACTH and A4 and the good disease control group with ACTH and A4 that is near normal or below normal ranges. Each group has elevated 17-OHP.

[0202] As shown in FIG. 4A, the baseline profile for the poor disease control group is above the blended gender based ULN of approximately 212 ng/dL. Treatment with compound 3 improves the A4 profile in subjects toward the blended gender based ULN of approximately 212

ng/dL. As shown in FIG. 4B, the baseline profile for the good disease control group is well below the blended gender based ULN of approximately 212 ng/dL. Treatment with compound 3 was able to further reduce A4 level compared to the baseline level. The small variation about the baseline likely representative of intra-subject daily variation.

Example 3 – Phase 2 Clinical Studies.

[0203] A Phase 2 Study is conducted involving a up to 52 weeks treatment multiple-dose study of Compound 3 and a glucocorticoid for the treatment of adults with classic CAH. After screening with the criteria disclosed herein, eligible patients are enrolled into up to 52 weeks of treatment followed by a 4-week washout/safety follow-up period.

[0204] The population are composed of subgroup one subjects, approximately n=30 with a dose of 200 mg and n=30 with placebo. Each subject receives Compound 3 or placebo and a glucocorticoid daily for up to 24 weeks in a double-blind manner. Compound 3 and a glucocorticoid are administered as an oral daily dose. Following the double-blind period, all subject will receive open label compound 3 at 200 mg. Patients self-administer Compound 3 for up to 52 weeks. After a minimum of 2 weeks of concomitant treatment of Compound 3 and a glucocorticoid, subjects are eligible for reductions in their glucocorticoid. Reduction occurs at 5 mg hydrocortisone equivalent increments over a period of 24 weeks with subjects eligible for up to 5 dose reductions prior to study end.

[0205] Study Design

- Study Type: Interventional
- Primary Purpose: Treatment
- Study Phase: Phase 2
- Interventional Study Model: double-blind (24 weeks) open-label (28 weeks)
- Allocation: Equal Randomization
- Enrollment: Up to approximately 60 [n=30 per group]

Outcome Measures

Primary Outcome Measure:

1. Reduction of glucocorticoid dose

Secondary Outcome Measure:

2. Assess normalization proportions for each key hormone
3. Assess impact of reductions of glucocorticoid dose on signs and symptoms of CAH
4. Assess impact of reductions of glucocorticoid dose on overall glucocorticoid toxicity Index.

Eligibility

- Minimum Age: 18 Years
- Maximum Age: 65
- Sex: All

- Gender Based: No
- Accepts Healthy Volunteers: No
- Criteria: Inclusion

Criteria:

Inclusion Criteria:

- Male and female patients age 18 or older.
- Documented diagnosis of classic CAH due to 21-hydroxylase deficiency
- Elevated A4 and ACTH <1.5x upper limit of normal at screening and baseline
- On a stable glucocorticoid replacement regimen for a minimum of 30 days

Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease
- Clinically significant psychiatric disorder.
- Clinically significant abnormal laboratory finding or assessment
- History of bilateral adrenalectomy or hypopituitarism
- Pregnant or nursing females
- Use of any other investigational drug within 30 days
- Unable to understand and comply with the study procedures, understand the risks, and/or unwilling to provide written informed consent.

[0206] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating Congenital Adrenal Hyperplasia (CAH), comprising administering a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof to a subject, wherein when said subject has a level of at least one steroid hormone that is less than two times an upper limit of a reference range of said at least one steroid hormone level , a dose of said steroid or a pharmaceutically acceptable salt thereof is reduced compared to a dose of said steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient that does not receive said CRF_1 antagonist or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein said subject has a level of a second and different steroid hormone that is less than two times an upper limit of a reference range of said second and different steroid hormone level.

3. The method of either claim 1 or claim 2, wherein said steroid hormone is selected from the group consisting of adrenocorticotropic hormone (ACTH), androstenedione (A4), 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, dehydroepiandrosterone, androstenediol, testosterone, dihydrotestosterone, estrone, estradiol, and estriol.

4. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than two times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than two times an upper limit of a reference range of ACTH.

5. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than two times an upper limit of a reference range of 17-OHP and a level of A4 that is less than two times an upper limit of a reference range of A4.

6. The method of one of claims 1-3, wherein said subject has a level of A4 that is less than two times an upper limit of a reference range of A4 and a level of ACTH that is less than two times an upper limit of a reference range of ACTH.

7. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.75 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.75 times an upper limit of a reference range of ACTH.

8. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.75 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.75 times an upper limit of a reference range of A4.

9. The method of one of claims 1-3, wherein said subject has a level of A4 that is less than 1.75 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.75 times an upper limit of a reference range of ACTH.

10. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.5 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.5 times an upper limit of a reference range of ACTH.

11. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.5 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.5 times an upper limit of a reference range of A4.

12. The method of one of claims 1-3, wherein said subject has a level of A4 that is less than 1.5 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.5 times an upper limit of a reference range of ACTH.

13. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.25 times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than 1.25 times an upper limit of a reference range of ACTH.

14. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than 1.25 times an upper limit of a reference range of 17-OHP and a level of A4 that is less than 1.25 times an upper limit of a reference range of A4.

15. The method of one of claims 1-3, wherein said subject has a level of A4 that is less than 1.25 times an upper limit of a reference range of A4 and a level of ACTH that is less than 1.25 times an upper limit of a reference range of ACTH.

16. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than one times an upper limit of a reference range of 17-OHP and a level of ACTH that is less than one times an upper limit of a reference range of ACTH.

17. The method of one of claims 1-3, wherein said subject has a level of 17-OHP that is less than one times an upper limit of a reference range of 17-OHP and a level of A4 that is less than one times an upper limit of a reference range of A4.

18. The method of one of claims 1-3, wherein said subject has a level of A4 that is less than one times an upper limit of a reference range of A4 and a level of ACTH that is less than one times an upper limit of a reference range of ACTH.

19. The method of any of claims 1-18, further comprising reducing said dose of said steroid or a pharmaceutically acceptable salt thereof in a 5 mg increment.

20. A method of treating Congenital Adrenal Hyperplasia (CAH), comprising administering a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 (CRF1) antagonist or a pharmaceutically acceptable salt thereof to a subject, wherein when said

subject has a level of at least one steroid hormone that is more than an upper limit of a reference range of said at least one steroid hormone level, a dose of said steroid or a pharmaceutically acceptable salt thereof is not reduced compared to a dose of said steroid or a pharmaceutically acceptable salt thereof administered to a CAH patient that does not receive said CRF1 antagonist or a pharmaceutically acceptable salt thereof.

21. The method of claim 20, wherein said subject has a level of said at least one steroid hormone that is more than two times an upper limit of a reference range of said at least one steroid hormone level.

22. The method of claim 20, wherein said subject has a level of said at least one steroid hormone that is more than 1.75 times an upper limit of a reference range of said at least one steroid hormone level.

23. The method of claim 20, wherein said subject has a level of said at least one steroid hormone that is more than 1.5 times an upper limit of a reference range of said at least one steroid hormone level.

24. The method of claim 20, wherein said subject has a level of said at least one steroid hormone that is more than 1.25 times an upper limit of a reference range of said at least one steroid hormone level.

25. The method of claim 20, wherein said steroid hormone is selected from the group consisting of adrenocorticotropic hormone (ACTH), androstenedione (A4), 17-hydroxyprogesterone (17-OHP), deoxycorticosterone, 11-deoxycortisol, cortisol, corticosterone, aldosterone, pregnenolone, 17α-hydroxy pregnenolone, progesterone, dehydroepiandrosterone, androstenediol, testosterone, dihydrotestosterone, estrone, estradiol, and estriol.

26. The method of any of claims 20-25, further comprising maintaining said dose of said steroid or a pharmaceutically acceptable salt thereof until said levels of at least two steroid hormones are less than 2 times said upper limit of said reference ranges of said two steroid hormones respectively.

27. The method of any of claims 20-25, further comprising reducing said dose of said steroid or a pharmaceutically acceptable salt thereof in a 5 mg increment when said levels of at least two steroid hormones are less than 2 times said upper limit of said reference ranges of said two steroid hormones respectively.

28. The method of claim 27, wherein said at least two steroid hormones comprise 17-OHP and ACTH.

29. The method of claim 27, wherein said at least two steroid hormones comprise 17-OHP and A4.

30. The method of claim 27, wherein said at least two steroid hormones comprise A4 and ACTH.

31. The method of any of claims 1-30, wherein said reference range of ACTH or A4 level of said subject is controlled by a factor selected from the group consisting of age, sex, menopausal status, laboratory setting, time of a day and combinations thereof.

32. The method of any of claims 1-30, wherein said level of ACTH or A4 is 2 times, 1.5 times, 1.25 times, or 1 times said upper limit of said normal range of ACTH or A4 level of said subject.

33. The method of any of claims 1-30, wherein said amount of said steroid or a pharmaceutically acceptable salt thereof comprises a range of about 10 mg to about 80 mg of hydrocortisone equivalents, wherein said steroid or a pharmaceutically acceptable salt thereof is administered daily.

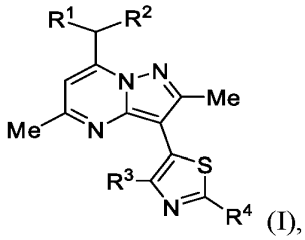
34. The method of any of claims 1-30, wherein said amount of said CRF_1 antagonist or a pharmaceutically acceptable salt thereof comprises a range of about 10 mg to about 200 mg, wherein said CRF_1 antagonist or a pharmaceutically acceptable salt thereof is administered daily.

35. The method of any of claims 1-34, wherein said subject is treated for a period of about 4 weeks to about 36 weeks.

36. The method of any of claims 1-34, wherein after said subject is treated for a period of about 4 weeks to about 36 weeks, said subject is reassessed to determine if a different method of treating CAH should be administered.

37. The method of any one of claims 1-36, wherein said CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003.

38. The method of any one of claims 1-37, wherein said CRF_1 antagonist is a compound of Formula (I):

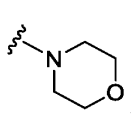
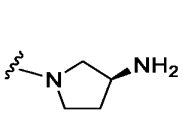
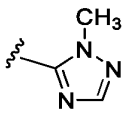
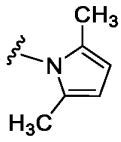


(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently ethyl or *n*-propyl;

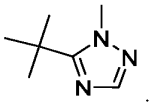
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

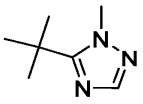
R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

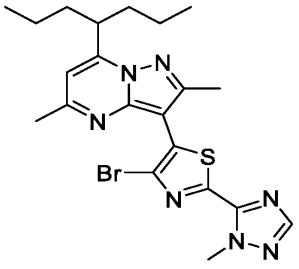
39. The method of claim 38, wherein R^3 is Cl, Br, methyl, or trifluoromethyl.

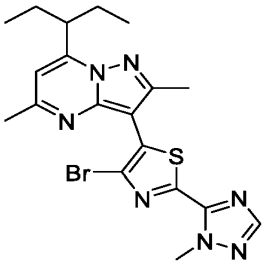
40. The method of claims 38 or 39, wherein R^3 is Cl, Br, or methyl.

41. The method of any one of claims 38-40, wherein R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  .

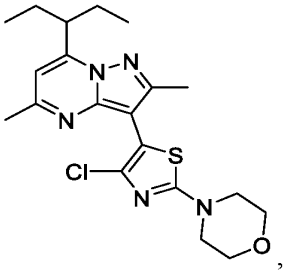
42. The method of any one of claims 38-40, wherein R^4 is morpholin-4-yl or  .

43. The method of any one of claims 38-40, wherein R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

44. The method of claim 38, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

45. The method of claim 38, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

46. The method of claim 38, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

47. The method of any one of claims 1-46, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg to about 200 mg total daily dose to the subject.

48. The method of any one of claims 1-46, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

49. The method of any one of claims 1-46, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject.

50. The method of any one of claims 1-46, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject.

51. The method of any one of claims 1-46, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 75 mg total daily dose to the subject.

52. The method of any one of claims 1-46, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject.

53. The method of any one of claims 1-46, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject.

54. The method of any one of claims 1-46, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is in the form of microparticles.

55. The method of claim 54, wherein the average size of the microparticles is between about 1 μm to about 20 μm.

56. The method of claim 54, wherein the average size of the microparticles is between about 5 μm to about 15 μm.

57. The method of claim 54, wherein the average size of the microparticles is less than about 10 μm.

58. The method of any one of claims 1-56, wherein the CRF1 antagonist or pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

59. The method of any one of claims 1-56, wherein the steroid or a pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition.

60. The method of claim 58 or 59, wherein the pharmaceutical composition is in the form of a capsule or a tablet.

61. The method of claim 60, wherein the capsule is a hard gelatin capsule.

62. The method of claim 60, wherein the capsule is a soft gelatin capsule.

63. The method of any one of claims 60-62, wherein the capsule is formed using materials selected from the group consisting of natural gelatin, synthetic gelatin, pectin, casein, collagen, protein, modified starch, polyvinylpyrrolidone, acrylic polymers, cellulose derivatives, and any combinations thereof.

64. The method of any one of claims 58-63, wherein the pharmaceutical composition is free of additional excipients.

65. The method of any one of claims 58-63, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

66. The method of claim 60, wherein the pharmaceutical composition is in the form of a tablet.

67. The method of claim 66, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

68. The method of any one of claims 1-66, wherein the steroid or pharmaceutically acceptable salt thereof is a glucocorticoid or a pharmaceutically acceptable salt thereof.

69. The method of claim 68, wherein the glucocorticoid or a pharmaceutically acceptable salt thereof is prednisone, cortisone, prednisolone, triamcinolone, methylprednisolone, betamethasone, dexamethasone, hydrocortisone or a pharmaceutically acceptable salt thereof.

70. The method of any one of claims 1-69, wherein levels of steroid hormones in the subject are determined from a biological sample from the subject.

71. The method of claim 70, wherein the biological sample is selected from the group of blood, blood fractions, plasma, serum, and saliva.

72. The method of claim 70, wherein the biological sample is obtained non-invasively.

73. The method of any one of claims 1-72, wherein said subject is tested in the morning.

74. The method of any one of claims 1-72, wherein said subject is tested to determine morning levels of A4 and ACTH.

75. The method of any one of claims 1-72, wherein the subject is a pediatric patient.

76. The method of any one of claims 1-72, wherein the subject is from about 0 years old to about 18 years old.

77. The method of any one of claims 1-72, wherein the subject is an adult patient.

78. The method of any one of claims 1-77, wherein the steroid and the CRF_1 antagonist are administered concurrently.

79. The method of any one of claims 1-77, wherein the steroid and the CRF_1 antagonist are administered in one pharmaceutical composition.

80. The method of any one of claims 1-77, wherein the steroid and the CRF_1 antagonist are administered concurrently in separate pharmaceutical compositions.

81. The method of any one of claims 1-77, wherein the steroid and the CRF_1 antagonist are administered sequentially.

82. The method of claim 81, wherein the steroid and the CRF_1 antagonist are administered sequentially within 24 hours.

83. The method of claim 81, wherein the steroid and the CRF_1 antagonist are administered sequentially within 8 hours.

84. The method of claim 81, wherein the steroid and the CRF_1 antagonist are administered sequentially within 2 hours.

85. The method of claim 81, wherein the steroid and the CRF_1 antagonist are administered sequentially within 10 minutes.

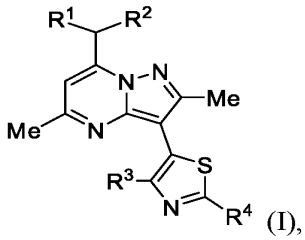
86. The method of any one of claims 1-85, wherein CAH is classic CAH.

87. The method of any one of claims 1-85, wherein CAH is non-classic CAH.

88. A composition comprises a steroid or a pharmaceutically acceptable salt thereof and a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof, wherein said CRF_1 antagonist or pharmaceutically acceptable salt thereof is selected from the group consisting of: Antalarmin hydrochloride, Pfizer CP 154526, CP 376395 hydrochloride, NBI 27914 hydrochloride, NBI 35965 hydrochloride, NGD 98-2 hydrochloride, Pexacerfont, R 121919 hydrochloride, SN003.

89. The composition of claim 88, wherein said a steroid or a pharmaceutically acceptable salt thereof is exogenous glucocorticoids (GC) or a pharmaceutically acceptable salt thereof.

90. The composition of either claim 88 or 89, wherein said CRF_1 antagonist is a compound of Formula (I):

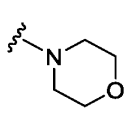
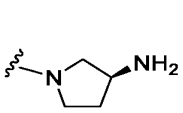
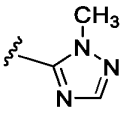
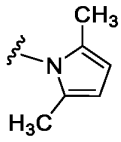


(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently ethyl or *n*-propyl;

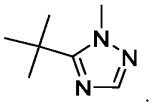
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

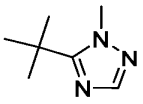
R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ,  , or  ; and

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

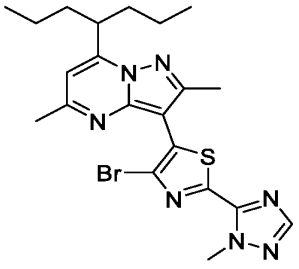
91. The composition of claim 90, wherein R^3 is Cl, Br, methyl, or trifluoromethyl.

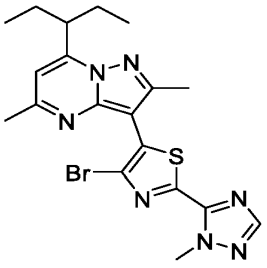
92. The composition of claims 90 or 91, wherein R^3 is Cl, Br, or methyl.

93. The composition of any one of claims 90-92, wherein R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  .

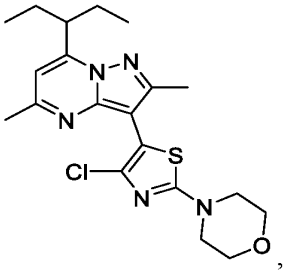
94. The composition of any one of claims 90-92, wherein R^4 is morpholin-4-yl or  .

95. The composition of any one of claims 90-92, wherein R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

96. The composition of claim 90, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

97. The composition of claim 90, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

98. The composition of claim 90, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

99. The composition of any one of claims 90-98, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg to about 200 mg total daily dose to the subject.

100. The composition of any one of claims 90-98, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 200 mg total daily dose to the subject.

101. The composition of any one of claims 90-98, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 150 mg total daily dose to the subject.

102. The composition of any one of claims 90-98, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 100 mg total daily dose to the subject.

103. The composition of any one of claims 90-98, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 75 mg total daily dose to the subject.

104. The composition of any one of claims 90-98, wherein the CRF_1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 50 mg total daily dose to the subject.

105. The composition of any one of claims 90-98, wherein the CRF1 antagonist or pharmaceutically acceptable salt is administered in a dose of about 25 mg total daily dose to the subject.

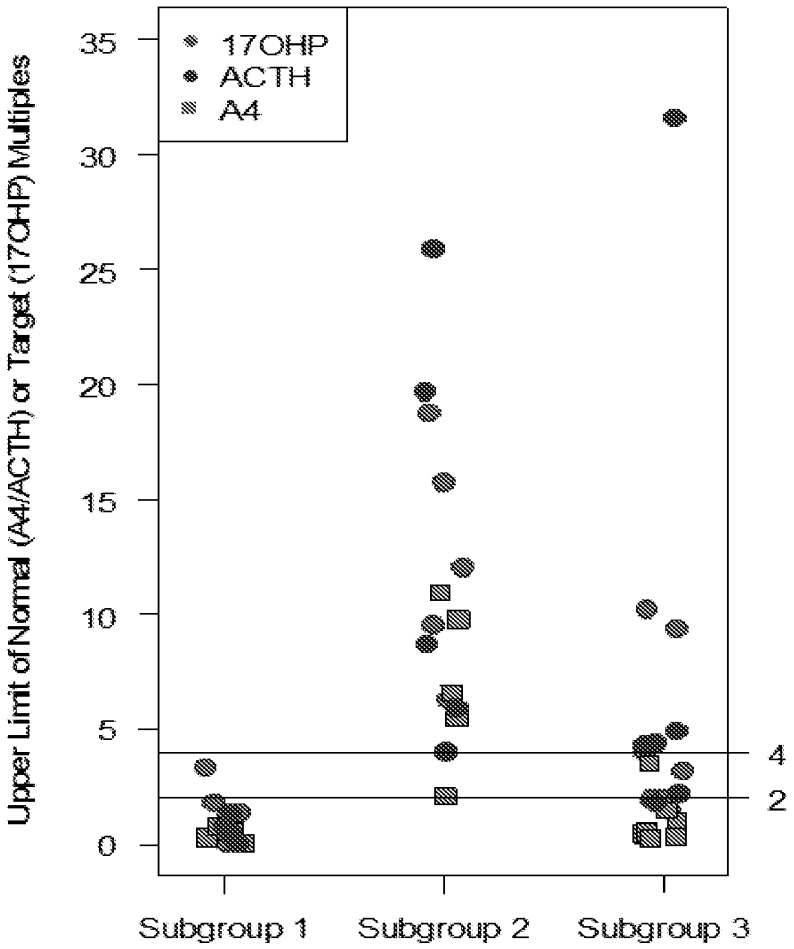

17OHP
ACTH
A4
Upper Limit of Normal (A4/ACTH) or Target (17OHP) Multiples
35
30
25
20
15
10
5
0
4
2
Subgroup 1
Subgroup 2
Subgroup 3

FIG. 1

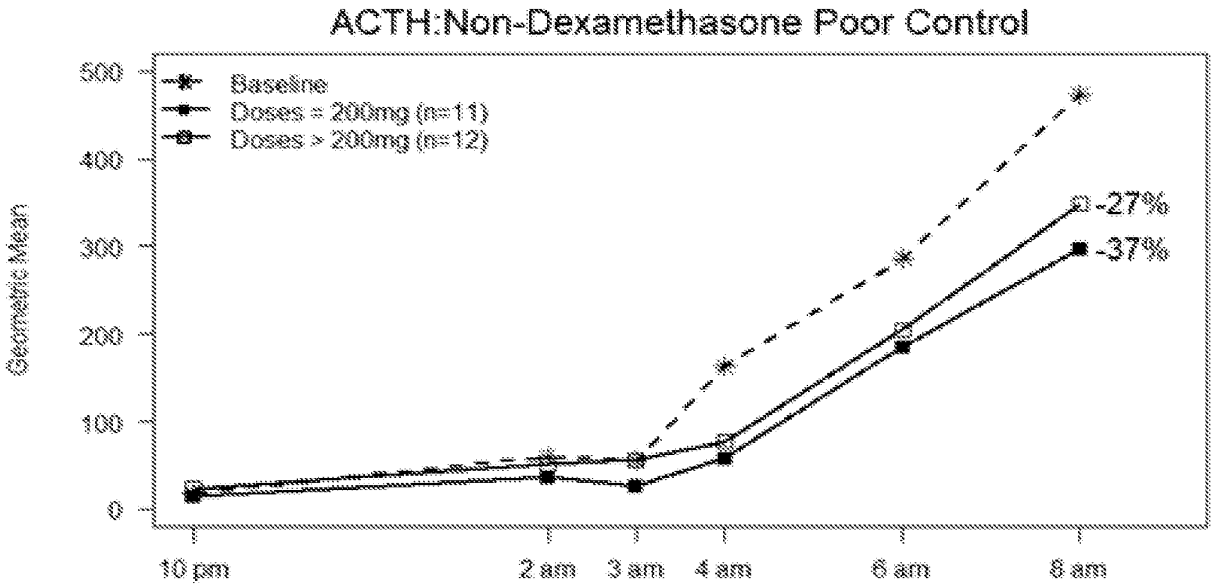

ACTH:Non-Dexamethasone Poor Control
Geometric Mean
500
400
300
200
100
0
Baseline
Doses = 200mg (n=11)
Doses > 200mg (n=12)
-27%
-37%
10 pm
2 am
3 am
4 am
6 am
8 am

FIG. 2A

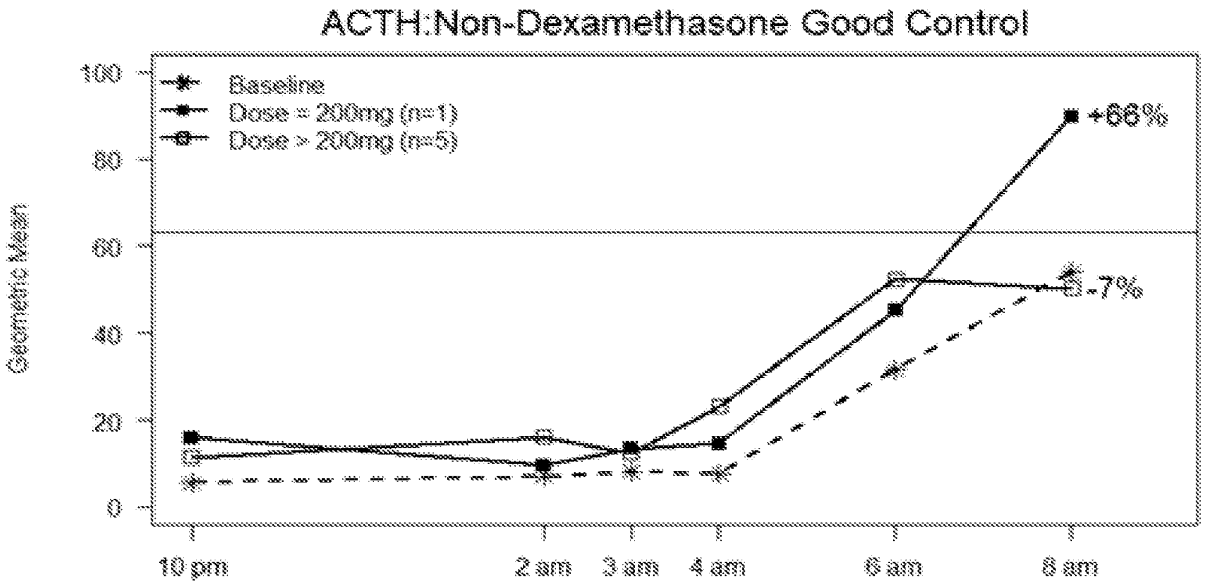

ACTH:Non-Dexamethasone Good Control
Geometric Mean
100
80
60
40
20
0
Baseline
Dose = 200mg (n=1)
Dose > 200mg (n=5)
+66%
-7%
10 pm
2 am
3 am
4 am
6 am
8 am

FIG. 2B

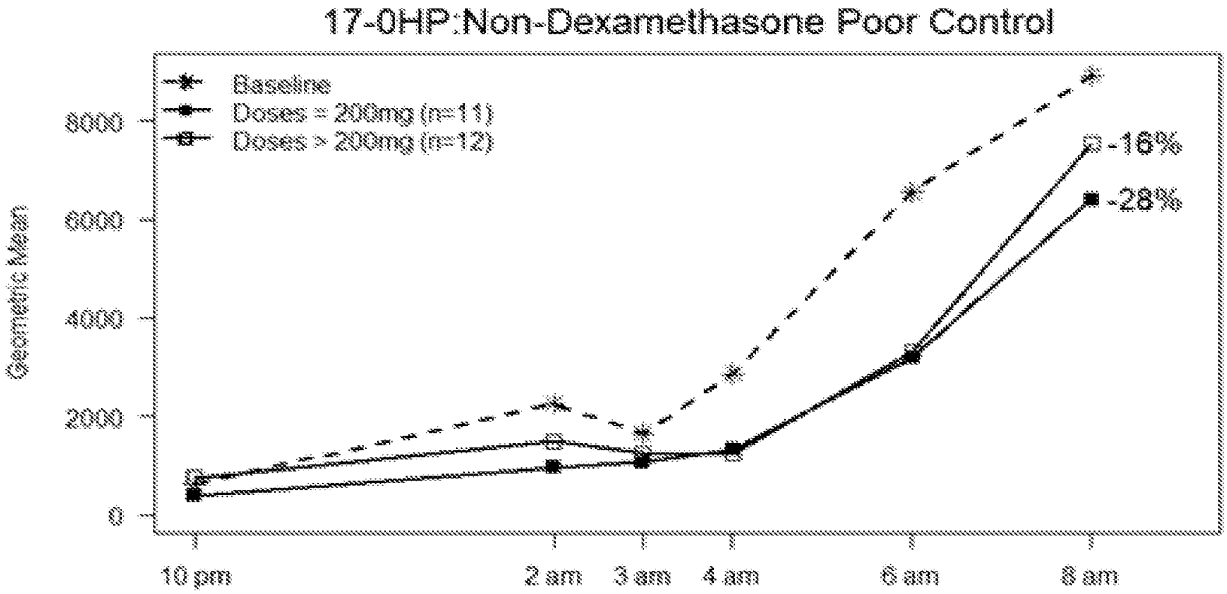

17-0HP:Non-Dexamethasone Poor Control
Baseline
Doses = 200mg (n=11)
Doses > 200mg (n=12)
Geometric Mean
8000
6000
4000
2000
0
10 pm
2 am
3 am
4 am
6 am
8 am
-16%
-28%

FIG. 3A

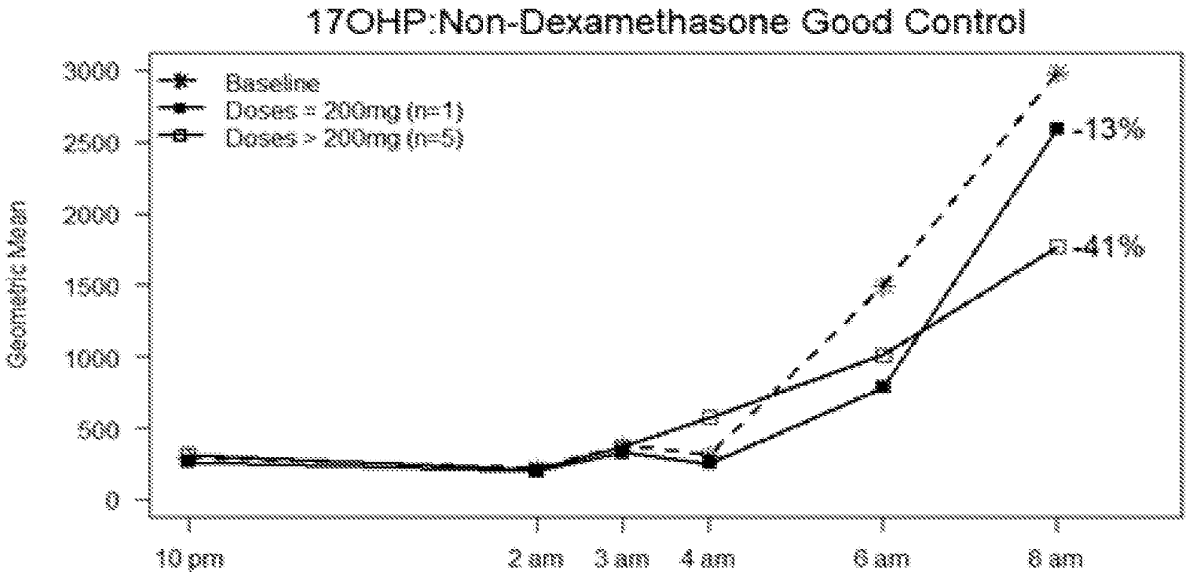

17OHP:Non-Dexamethasone Good Control
Baseline
Doses = 200mg (n=1)
Doses > 200mg (n=5)
Geometric Mean
3000
2500
2000
1500
1000
500
0
10 pm
2 am
3 am
4 am
6 am
8 am
-13%
-41%

FIG. 3B

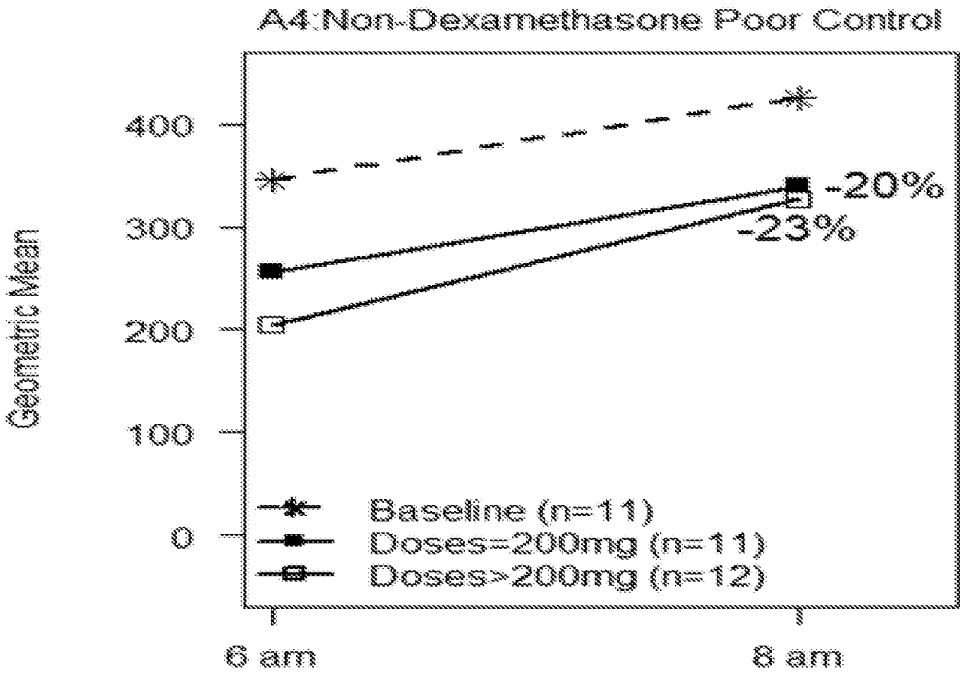

A4:Non-Dexamethasone Poor Control
Geometric Mean
400
300
200
100
0
-20%
-23%
Baseline (n=11)
Doses=200mg (n=11)
Doses>200mg (n=12)
6 am
8 am

FIG. 4A

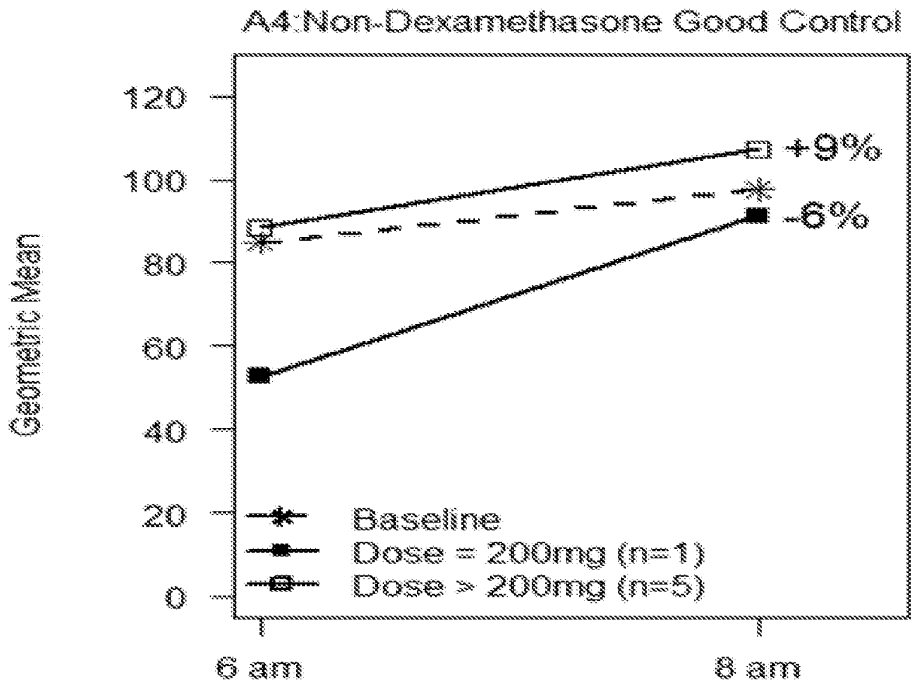

A4:Non-Dexamethasone Good Control
Geometric Mean
120
100
80
60
40
20
0
+9%
-6%
Baseline
Dose = 200mg (n=1)
Dose > 200mg (n=5)
6 am
8 am

FIG. 4B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/042820

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/56(2006.01)i, A61K 31/57(2006.01)i, A61K 38/22(2006.01)i, A61K 31/519(2006.01)i, A61K 31/5377(2006.01)i, A61P 5/38(2006.01)i, C07D 487/04(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/56; A61K ; A61K 31/4412; A61K 31/4545; A61K 31/519; A61P 25/24; A61K 31/57; A61K 38/22; A61K 31/5377; A61P 5/38; C07D 487/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & keywords: Congenital Adrenal Hyperplasia (CAH), corticortropin-releasing factor type-1 (CRF1) antagonist

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2017-0020877 A1 (NEUROCRINE BIOSCIENCES, INC.) 26 January 2017 claims 14-18; TABLE 2; paragraphs [0054], [0070], [0086]	88-91,96-98
X	WO 2005-020910 A2 (PHARMACIA CORPORATION) 10 March 2005 claims 1-5	88-91,96-98
A	US 2011-0136865 A1 (BUNTINX, E.) 09 June 2011 the whole document	88-91,96-98
A	WO 2013-160317 A2 (HOLSBOERMASCHMEYER NEUROCHEMIE GMBH) 31 October 2013 the whole document	88-91,96-98

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 2020 (24.11.2020)	**25 November 2020 (25.11.2020)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
Jung, Da Won
Telephone No. +82-42-481-5373

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2020/042820

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2017-0020877 A1	26/01/2017	CN 106102740 A	09/11/2016
		CN 111228274 A	05/06/2020
		EP 3096756 A1	30/11/2016
		JP 2017-503030 A	26/01/2017
		JP 2019-081814 A	30/05/2019
		JP 6585625 B2	02/10/2019
		KR 10-2016-0106176 A	09/09/2016
		US 2019-0231781 A1	01/08/2019
		WO 2015-112642 A1	30/07/2015
WO 2005-020910 A2	10/03/2005	US 2005-0085479 A1	21/04/2005
		WO 2005-020910 A3	09/06/2005
US 2011-0136865 A1	09/06/2011	EP 1708790 A1	11/10/2006
		EP 1708790 B1	21/04/2010
		EP 2272514 A1	12/01/2011
		US 2007-0078162 A1	05/04/2007
		US 2011-0207776 A1	25/08/2011
		US 8304431 B2	06/11/2012
		WO 2005-053796 A1	16/06/2005
WO 2013-160317 A2	31/10/2013	EP 2841068 A2	04/03/2015
		EP 2841068 B1	28/11/2018
		JP 2015-516979 A	18/06/2015
		US 2015-0094310 A1	02/04/2015
		WO 2013-160317 A3	03/01/2014

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/042820

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-87
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-87 pertain to methods for treatment of the human body and thus relate to a subject-matter which this International Searching Authority is not required to search under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv).

2. ☒ Claims Nos.: 39,44-46,55-57,61,62,66,67,69,71,72,82-85
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 39,44-46,55-57,61,62,66,67,69,71,72,82-85 are regarded to be unclear because they refer to claims 38,54,60,66,68,70,81, which does not comply with PCT Rule 6.4(a).

3. ☒ Claims Nos.: 4-19,31-38,40-43,47-54,58-60,63-65,68,70,73-81,86,87,92-95,99-105
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,303	**08/18/2025 02:16:56 PM Z ET**	**50535-710.305**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1040	FILED BY	Colleen Mensching
PATENT CENTER #	71902331	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Victoria Cheng

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710.305 - POA.pdf	2	Power of Attorney	355 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Spruce 50535-710.305 - POA.pdf	28CF196DBA249CEFCC906AE7EE5D1EDF8B91EFD5159058D9D4B51E1A12B7BE2DAE1BD63BC12618BC59ADCF65C26496BFA733FC3EC7B684591147BAE65E7B4A65

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 09/30/2025. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	19/043,303
Filing Date	01/31/2025
First Named Inventor	Alexis HOWERTON
Title	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS
Art Unit	1627
Examiner Name	Sarah PIHONAK
Attorney Docket Number	50535-710.305

SIGNATURE of Applicant or Patent Practitioner

Signature	/Victoria Cheng/	Date (Optional)	2025-08-18
Name	Victoria Cheng	Registration Number	79,641
Title (if Applicant is a juristic entity)	Patent Practitioner		
Applicant Name (if Applicant is a juristic entity)	Spruce Biosciences, Inc.		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of 1 forms are submitted.

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 09/30/2025. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 21971

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Spruce Biosciences, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Signed by: Samir Gharib A1BFEB34D8F9452...	Date (Optional)	11-Aug-2025
Name	Samir Gharib		
Title	President and CFO		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 1 forms are submitted.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
19/043,303	01/31/2025	Alexis HOWERTON	50535-710.305

CONFIRMATION NO. 1040

21971
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

POA ACCEPTANCE LETTER

Date Mailed: 08/20/2025

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/18/2025.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/snguyen/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/043,303	01/31/2025	Alexis HOWERTON	50535-710.305	1040

21971 7590 09/05/2025

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
PIHONAK, SARAH	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
09/05/2025	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary	**Application No.** 19/043,303	**Applicant(s)** HOWERTON et al.	
	Examiner SARAH PIHONAK	**Art Unit** 1627	**AIA (First Inventor to File) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 1/31/2025.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-19 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-19 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 1/31/2025 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Priority

This application, filed 01/31/2025 is a Continuation of 18941832, filed 11/08/2024

18941832 is a Continuation of 17667285, filed 02/08/2022, now abandoned.

17667285 is a Continuation of 17081694, filed 10/27/2020, now U.S. Patent # 11304950.

17081694 is a Continuation of PCT/US2019/029486, filed 04/26/2019.

PCT/US2019/029486 Claims Priority from Provisional Application 62822815, filed 03/23/2019.

PCT/US2019/029486 Claims Priority from Provisional Application 62663951, filed 04/27/2018.

Status of Claims

1. Claims 1-19 are currently pending. A track one status has been granted.

2. Claims 1-19 were examined and are rejected.

Claim Rejections-35 USC § 112

3. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-19 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Claims 18 and 19 both depend from claim 1 and recite "the biomarker". However, claim 1 doesn't refer to a biomarker. There is insufficient antecedent basis for this limitation in the claims.

To overcome this rejection, it is suggested these claims be amended to depend from claim 17, which recites a biomarker.

Claim Rejections-Nonstatutory Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed.

Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely

online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

Claims 1-19 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 and 19 of U.S. Patent No. 11304950 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass administering a CRF1 antagonist to a subject having an ovarian adrenal rest tumor (OART) or a testicular adrenal rest tumor (TART). Although the instant claims recite changing a metabolic parameter and the patented claims don't explicitly recite this limitation, it would have been prima facie obvious that by administering a CRF1 antagonist to the same patient population, a subject having an OART or a TART, the same results would have been achieved by practicing the method of the patented claims. Furthermore, both sets of claims recite a dose of CRF1 antagonist between about 10-400 mg/day (patented claim 13 & instant claim 8); oral administration (patented claim 14 & instant claim 15); and wherein the CRF1 antagonist is formulated as a capsule or tablet (patented claim 15 & instant claim 16). Therefore, the instant and patented claims are not patentably distinct.

5. Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 72-83 and 85-91 of copending Application No. 18941832 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass administering a CRF1

antagonist to a subject having an ovarian adrenal rest tumor or a testicular adrenal rest tumor. In particular, the copending claims recite treating a benign tumor by administering a CRF1 antagonist, and further specify wherein the benign tumor is an ovarian adrenal rest tumor or a testicular adrenal rest tumor (copending claim 75). Additionally, both sets of claims recite reducing the plasma concentration of a biomarker comprising 17-OHP, ACTH, testosterone, androstenedione, luteinizing hormone, FSH, inhibin B, SHBG, renin, or aldosterone (see copending claim 86 & instant claim 17); oral administration (copending claim 85 & instant claim 15); wherein the CRF1 antagonist is formulated as a capsule or tablet (copending claim 91 & instant claim 16). Furthermore, the amount of CRF1 antagonist administered in the copending claims overlaps with the amount range recited by the instant claims (see instant claim 8 for 10-400 mg/day, compared to copending claim 78 for 5-800 mg/day). Although the instant claims recite changing a metabolic parameter and the copending claims don't explicitly recite this limitation, it would have been prima facie obvious that by administering a CRF1 antagonist to the same patient population, a subject having an ovarian adrenal rest tumor or a testicular adrenal rest tumor, the same results would have been achieved by practicing the method of the copending claims.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

6. Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 and 17-21 of copending application 19043264 in view

of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003. Although the claims at issue are not identical, they are not patentably distinct from each other because both sets of claims encompass administering a CRF1 antagonist to a subject having an ovarian adrenal rest tumor and CAH (see instant and copending claims 1 and 5). The instant and copending claims differ from each other as the instant claims are not drawn to treating not menstrual irregularities as recited by the copending claims. However, Stikkelbroeck teaches females with CAH can have irregular menstrual cycles due to adrenal androgen excess (p. 1030, 1st para). Stikkelbroeck further teaches females with CAH can develop adrenal rest tumors in the ovaries which replace normal ovarian tissue, causing impaired menstrual cycling (p. 1034, right col., last para-p. 1035, left col., top para). Therefore, it would have been prima facie obvious to have applied the instantly claimed method to treat menstrual irregularities in a subject with CAH and ovarian adrenal rest tumors, and have had a reasonable expectation of success. Moreover, it would have been prima facie obvious that by administering the same CRF1 antagonist to treat the same patient population, infertility as recited by copending claim 4 would have also been treated.

Although the copending claims don't explicitly recite changing a metabolic parameter of a subject having an OART, it would have been prima facie obvious that by administering a CRF1 antagonist to the same patient population, a subject having an OART, the same changes in metabolic parameters would have been achieved by practicing the method of the copending claims.

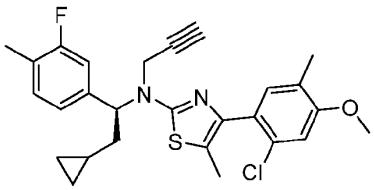
Additionally, the amount of CRF1 antagonist administered is the same (10-400 mg/day as recited by instant and copending claim 8); wherein the CRF1 antagonist is formulated as a

capsule or tablet (see copending claim 18 & instant claim 16); wherein the CRF1 antagonist is administered once per day (copending claim 13 & instant claim 13); and the CRF1 antagonist is administered twice per day (copending claim 14 & instant claim 14). Both sets of claims explicitly recite the same CRF1 antagonists (see copending claim 1 & instant claim 1). As CAH affects females, including women and adolescent females (see Stikkelbroeck, p. 1030, right col., last para-p. 1031, left col., top para), it would have been prima facie obvious to have applied the instantly claimed method to treat an adolescent female as recited by copending claim 6, and a female at least 18 years or older as recited by copending claim 7. For these reasons the instant and copending claims are obvious variants of each other and are not patentably distinct.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claim Objection

Claims 1 and 3 are objected to because of the following informalities: the claims show a compound that has functional group indicating a carbon atom with 5 bonds. See shown compound:



Appropriate correction is required.

Information Disclosure Statements

7. The IDS filed on 2/5/25 and 8/13/25 have been considered.

Conclusion

8. Claims 1-19 were examined and are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached Monday-Friday 9:00-5:30 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney Klinkel can be reached at 571-270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SARAH . PIHONAK
Primary Examiner

Art Unit 1627

/SARAH PIHONAK/
Primary Examiner, Art Unit 1627

Notice of References Cited	Application/Control No. 19/043,303	Applicant(s)/Patent Under Reexamination HOWERTON et al.	
	Examiner SARAH PIHONAK	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
	A					
	B					
	C					
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	E					
	F					
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FOREIGN PATENT DOCUMENTS

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	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title, Date, Publisher, Edition or Volume, Pertinent Pages
	U	Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003 (Year: 2003)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/043,303	HOWERTON et al.
	Examiner	Art Unit
	SARAH PIHONAK	1627

CPC - Searched*		
Symbol	Date	Examiner
a61k31/519,5377; a61p5/06,08; a61p35/00	09/02/2025	s.p.

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
a61k31/519,5377; a61p5/06,08; a61p35/00	09/02/2025	s.p.
inventor & applicant search in PE2E, patent data portal	09/02/2025	s.p.
invention & claims search in PE2E (incl. similarity search), stnext	09/02/2025	s.p.

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/SARAH PIHONAK/ Primary Examiner, Art Unit 1627	

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	19	("10849908" OR "11007201" OR "11304950" OR "11311549" OR "11344557" OR "11351177" OR "12115166" OR "20100196389" OR "20100222339" OR "20170020877" OR "20220143037" OR "20220211711" OR "4328245" OR "4409239" OR "4410545" OR "4861760" OR "4911920" OR "5212162" OR "5403841").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2025/05/07 05:21 PM
L2	127	((testicular OR testicle OR ovarian OR ovary) WITH adrenal WITH rest WITH tumor*) AND (corticotropin adj10 releasing adj10 factor adj10 (antagon* OR block*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/05/07 05:53 PM
L3	1	"20250195527".pn.	(US-PGPUB)	OR	ON	ON	2025/09/02 04:12 PM
L4	28	(Artificial Intelligence) More like doc: US-20250195527-A1 Text: (JP-H0971528-A OR WO-2007109853-A1 OR BR-PI0717023-B8 OR US-20100203048-A1 OR CN-106102740-A OR TW-202400179-A OR EA-202090450-A1 OR US-20250195527-A1 OR US-20250177403-A1 OR	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO;	OR	ON	ON	2025/09/02 04:12 PM

		EP-3784233-B1 OR HK-40040045-A OR US-20250177404-A1 OR HK-40040045-B OR AU-2023203095-A1 OR CA-3098562-A1 OR US-20220211711-A1 OR US-11304950-B2 OR US-20240285593-A1 OR US-20250064812-A1 OR US-11304952-B2).did.	JPO; DERWENT; IBM_TDB)				
L5	11	L4 AND ((testicular OR ovar*) adj10 adrenal adj10 rest adj10 (tumor OR neoplasm))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/09/02 04:16 PM
L6	86	(a61k31/519,5377 OR a61p5/06,08 OR a61p35/00).cpc. AND ((testicular OR ovar*) adj10 adrenal adj10 rest adj10 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/09/02 04:18 PM
L7	35	((("Spruce") near3 ("Biosciences") near3 ("Inc"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2025/09/02 04:21 PM
L8	24	((("HOWERTON") near3 ("Alexis")) OR (("GERBER") near3 ("Hal"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2025/09/02 04:22 PM
L9	11	(L7 OR L8) AND ((testicular OR ovar*) adj10 adrenal adj10 rest adj10 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2025/09/02 04:22 PM

L10	42	(corticotropin adj10 releas* adj10 factor adj10 (antagon* OR inhibit* OR suppress* OR reduc* OR decreas*)) AND ((testicular OR ovar*) adj10 adrenal adj10 rest adj10 (tumor* OR neoplasm*))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2025/09/02 04:24 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	9	Attorney Docket Number	50535-710.306

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	EP-3784233-B1	06-05-2024	SPRUCE BIOSCIENCES INC [US]		☐

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Examiner Signature	/SARAH PIHONAK/	Date Considered	09/02/2025

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Doc description: Information Disclosure Statement (IDS) Filed

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,264
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	2	of	9	Attorney Docket Number	50535-710.306

NON-PATENT LITERATURE DOCUMENTS			
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	001	AUCHUS, Richard J. et al. Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. New England Journal of Medicine 391(6):504-514 (2024).	☐
	002	AUCHUS, Richard J. et al. Supplemental Information: Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. New England Journal of Medicine 391(6):504-514 (2024).	☐
	003	AUCHUS, Richard J. Management Considerations for the Adult With Congenital Adrenal Hyperplasia. Molecular and Cellular Endocrinology 408:190-197 (2015).	☐
	004	AVILA, N. A. et al. Testicular adrenal rest tissue in congenital adrenal hyperplasia: serial sonographic and clinical findings. AJR. American journal of roentgenology 172(5):1235-1238 (1999).	☐
	005	AYCAN, Zehra et al. Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia. Clinical endocrinology 78(5):667-672 (2013).	☐
	006	CLAAHSEN-VAN DER GRINTEN, H. L. et al. Testicular adrenal rest tumours in congenital adrenal hyperplasia. International Journal of pediatric endocrinology 2009:624823, 1-8 (2009).	☐
	007	CLAAHSEN-VAN DER GRINTEN, Hedi L. et al. Prevalence of testicular adrenal rest tumours in male children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. European journal of endocrinology 157(3):339-344 (2007).	☐
	008	CLAAHSEN-VAN DER GRINTEN, Hedi L. et al. Repeated successful induction of fertility after replacing hydrocortisone with dexamethasone in a patient with congenital adrenal hyperplasia and testicular adrenal rest tumors. Fertility and Sterility 88(3):705.e5-705.e8 (2007).	☐

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	009	ClinicalTrials.gov Identifier: NCT04457336. A Ph2b to Evaluate Clinical Efficacy and Safety of Tildacerfont in Adult CAH, Record created June 25, 2020. pp. 1-17. [retrieved on 2025-08-12] Available at URL: https://clinicaltrials.gov/study/NCT04457336.	☐
	010	DELFINO, Michele et al. Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia: prevalence and sonographic, hormonal, and seminal characteristics. Journal of ultrasound in medicine 31(3):383-388 (2012).	☐
	011	ENGELS, Manon et al. Testicular adrenal rest tumors: current insights on prevalence, characteristics, origin, and treatment. Endocrine Reviews 40(4):973-987 (2019).	☐
	012	EP19793181.9 Brief Communication - Opposition Proceedings dated August 5, 2025.	☐
	013	EP19793181.9 Reply from the opponent to submission of proprietor dated July 18, 2025.	☐
	014	EP19793181.9 Reply of the Patent Proprietor to the notice(s) of opposition dated June 18, 2025.	☐
	015	FLECK, Beth A. et al. Binding Kinetics Redefine the Antagonist Pharmacology of the Corticotropin-releasing Factor Type 1 Receptor. The Journal of Pharmacology and Experimental Therapeutics 341(2):518-531 (2012).	☐
	016	JOSEPH, Dana N., and Shannon Whirledge. Stress and the HPA axis: balancing homeostasis and fertility. International journal of molecular sciences 18(10):2224, 1-15 (2017).	☐
	017	MA, Li et al. Sonographic features of the testicular adrenal rests tumors in patients with congenital adrenal hyperplasia: a single-center experience and literature review. Orphanet Journal of Rare Diseases 14(1):242, 1-8 (2019).	☐

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	018	MAZZILLI, Rossella et al. The High Prevalence of Testicular Adrenal Rest Tumors in Adult Men With Congenital Adrenal Hyperplasia Is Correlated With ACTH Levels. Front Endocrinol (Lausanne) 10:335 (2019).	☐
	019	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Defence dated March 13, 2025 (Claim No. HP-2025-000005) (pp. 1-3).	☐
	020	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Grounds of Invalidity dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	021	Neurocrine Biosciences, Inc. (Claimant) v. Spruce Biosciences, Inc. (Defendant). Particulars of Claim dated January 31, 2025 (Claim No. HP-2025-000005) (pp. 1-10).	☐
	022	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Patent Owner's Response in U.S. Patent No. 12,115,166 dated July 8, 2025 (pp 1-6) (PGR-2025-00032).	☐
	023	Neurocrine Biosciences, Inc. (Plaintiff) v. Spruce Biosciences, Inc. (Defendant). Memorandum dated June 9, 2025 (Case No. 1:25-cv-00059-JDW (pp. 1-10).	☐
	024	NISSEN, Trygve et al. The clinical case report: a review of its merits and limitations. BMC Research Notes 7:264, 1-7 (2014).	☐
	025	REISCH, Nicole et al. High prevalence of reduced fecundity in men with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 94(5):1665-1670 (2009).	☐
	026	Spruce Biosciences announces topline results from CAHMELIA-203 in adult classic CAH and CAHPTAIN-205 in pediatric classic CAH. Spruce Biosciences :1-7 (2024).	☐

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	027	Spruce Biosciences announces topline results from CAHMELIA-204 in adult CAH and CAHPTAIN-205 in adult and pediatric CAH. Spruce Biosciences :1-4 (2024).	☐
	028	STIKKELBROECK, Nike M. M. L. et al. High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and Leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. The Journal of Clinical Endocrinology and Metabolism 86(12):5721-5728 (2001).	☐
	029	The Journal of Clinical Endocrinology and Metabolism Author Guidelines. Oxford Academic (2025); [retrieved on 2025-06-09]. Available at URL: https://academic.oup.com/jcem/pages/author_guidelines.	☐
	030	TURCU, Adina F. and Richard J. Auchus. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinology and Metabolism Clinics 44(2):275-296 (2015).	☐
	031	TURCU, Adina F., and Richard J. Auchus. Novel treatment strategies in congenital adrenal hyperplasia. Current Opinion in Endocrinology, Diabetes and Obesity 23(3):225-232 (2016).	☐
	032	TURCU, Adina F. et al. Supplemental Information: Single-dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. The Journal of Clinical Endocrinology and Metabolism 101(3):1174-1180 (2016).	☐
	033	U.S. Provisional Application No. 62/822,815 filed on March 23, 2019.	☐
	034	WALDRON, James. Spruce saws off only drug after 2nd hyperplasia fail, leaving biotech's direction in doubt. Fierce Biotech :1-2 (2024).	☐
	035	WANG, Zhu et al. Diagnosis of testicular adrenal rest tumors on ultrasound: a retrospective study of 15 cases report. Medicine 94(36):e1471, 1-6 (2015).	☐

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	036	World Health Organization Drug Information, 32(2):369-370 (2018).	☐
	037	YAMADA, Yasuki et al. New class of corticotropin-releasing factor (CRF) antagonists: small peptides having high binding affinity for CRF receptor. Journal of medicinal chemistry 47(5):1075-1078 (2004).	☐
	038	YASIR, Muhammad et al. Corticosteroid Adverse Effects. StatPearls, July 3, 2023; [retrieved on 2025-06-17]. Available at URL: https://www.ncbi.nlm.nih.gov/books/NBK531462/ pp. 1-14.	☐
	039	YU, Min Kyung et al. Clinical manifestations of testicular adrenal rest tumor in males with congenital adrenal hyperplasia. Annals of pediatric endocrinology and metabolism 20(3):155-161 (2015).	☐

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Sheet	7	of	9	Attorney Docket Number	50535-710.306

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☐ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

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SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Kaia R. Parenti/	Date (YYYY-MM-DD)	2025-08-13
Name/Print	Kaia R. Parenti	Registration Number	81050

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Sheet	8	of	9	Attorney Docket Number	50535-710.306

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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IT   50-02-2, Dexamethasone   50-23-7, Hydrocortisone   50-24-8, Prednisolone
     53-03-2, Prednisone   53-06-5, Cortisone   83-43-2, Methylprednisolone
     124-94-7, Triamcinolone   127-31-1, Fludrocortisone   378-44-9,
     Betamethasone   4419-39-0, Beclomethasone   51333-22-3, Budesonide
     157284-96-3   195055-03-9   202579-74-6   268545-87-5   752253-39-7
     885220-61-1   1014982-94-5   1014982-96-7   1802256-84-3, SSR 126374
     RL: PAC (Pharmacological activity); SCLM (Substance claimed); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (methods for treating testicular and ovarian
        adrenal rest tumors)

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 AU 2019260793 B2    AU 2019-260793        Register
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 BR 112020024062 A2  BR 2020-112020024062  Register
 CA 3098562 A1       CA 2019-3098562       Register
 CN 112423747 A      CN 2019-80043623      Register|Global Dossier
 EP 3784233 A1       EP 2019-793181        Register|Federated Reg.
 EP 3784233 B1       EP 2019-793181        Register|Federated Reg.
 EP 3784233 C0       EP 2019-793181        Register|Federated Reg.
 EP 4438124 A2       EP 2024-179880        Register|Federated Reg.
 EP 4438124 A3       EP 2024-179880        Register|Federated Reg.
 ES 2991516 T3       ES 2019-793181        Register
 JP 2021522340 T     JP 2021-509725        Register|Global Dossier
 JP 7427655 B2       JP 2021-509725        Register|Global Dossier
 MX 2020011344 A     MX 2020-11344         Register
 US 11304950 B2      US 2020-17081694      Register|Global Dossier
 US 20210038604 A1   US 2020-17081694      Register|Global Dossier
 US 20220211711 A1   US 2022-17667285      Register|Global Dossier
 US 20250064812 A1   US 2024-18941832      Register|Global Dossier
 US 20250177403 A1   US 2025-19043264      Register|Global Dossier
 US 20250177404 A1   US 2025-19043275      Register|Global Dossier
 US 20250195527 A1   US 2025-19043303      Register|Global Dossier
 WO 2019210266 A1    WO 2019-US29486       Register|Global Dossier

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     (FILE 'HOME' ENTERED AT 16:28:12 ON 02 SEP 2025)

     FILE 'CAPLUS' ENTERED AT 16:28:44 ON 02 SEP 2025
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               SET EXPAND CONTINUOUS
               E E3+ALL/CT
L2          2378 S E18-E25
               E  "ADRENAL REST TUMORS"/CT
               E E28+ALL/CT
L3             7 S E39
L4             1 S OVARIAN ADRENAL REST TUMORS/IT
L5            27 S TESTICULAR ADRENAL REST TUMORS/IT
L6            17 S (OVAR? (L) ADRENAL (L) REST (L) (TUMOR? OR NEOPLASM?))
L7            93 S (TESTIC? (L) ADRENAL (L) REST (L) (TUMOR? OR NEOPLASM?))

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L8                 STRUCTURE UPLOADED
L9             2 S L8 SSS SAM
L10           17 S L8 SSS FULL

     FILE 'CAPLUS' ENTERED AT 16:38:50 ON 02 SEP 2025
L11           14 S L10
L12            2 S L11 AND (L3 OR L4 OR L5 OR L6 OR L7)

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L13                STRUCTURE UPLOADED
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L15         3008 S L13 SSS FULL
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     FILE 'REGISTRY' ENTERED AT 16:43:28 ON 02 SEP 2025
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L20          564 S L18 SSS FULL

     FILE 'CAPLUS' ENTERED AT 16:46:58 ON 02 SEP 2025
L21           46 S L20
L22            1 S L21 AND (L3 OR L4 OR L5 OR L6 OR L7)

     FILE 'REGISTRY' ENTERED AT 16:47:33 ON 02 SEP 2025
L23               STRUCTURE UPLOADED
L24            4 S L23 SSS SAM
L25           41 S L23 SSS FULL

     FILE 'CAPLUS' ENTERED AT 16:51:03 ON 02 SEP 2025
L26          218 S L25
L27            1 S L26 AND (L3 OR L4 OR L5 OR L6 OR L7)

     FILE 'REGISTRY' ENTERED AT 16:51:45 ON 02 SEP 2025
L28               STRUCTURE UPLOADED
L29            2 S L28 SSS SAM
L30           47 S L28 SSS FULL

     FILE 'CAPLUS' ENTERED AT 16:54:57 ON 02 SEP 2025
L31           62 S L30
L32            2 S L31 AND (L3 OR L4 OR L5 OR L6 OR L7)

     FILE 'REGISTRY' ENTERED AT 16:56:02 ON 02 SEP 2025
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                 E SSR 126374/CN
L33            1 S E54

     FILE 'CAPLUS' ENTERED AT 16:56:32 ON 02 SEP 2025
L34            2 S L33
L35            2 S L2 AND (L3 OR L4 OR L5 OR L6 OR L7)

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	1	of	9	Attorney Docket Number	50535-710.305

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-4328245	05-04-1982	YU; Cheng-Der et al.	
	002	US-4409239	10-11-1983	YU; Cheng-Der	
	003	US-4410545	10-18-1983	YU; Cheng-Der et al.	
	004	US-4861760	08-29-1989	MAZUEL; Claude et al.	
	005	US-4911920	03-27-1990	JANI; Rajni et al.	
	006	US-5212162	05-18-1993	MISSEL; Paul J. T. et al.	
	007	US-5403841	04-04-1995	LANG; John C. et al.	
	008	US-10849908	12-01-2020	HOWERTON; Alexis et al.	
	009	US-11007201	05-18-2021	HOWERTON; Alexis et al.	
	010	US-11304950	04-19-2022	HOWERTON et al.	
	011	US-11311549	04-26-2022	HOWERTON; Alexis et al.	
	012	US-11344557	05-31-2022	HOWERTON; Alexis et al.	
	013	US-11351177	06-07-2022	HOWERTON; Alexis et al.	
	014	US-12115166	10-15-2024	HOWERTON; Alexis et al.	
	015	US-20100196389	08-05-2010	EVANS-FREKE; Stephen	
	016	US-20100222339	09-02-2010	CHEN; Zhaogen et al.	
	017	US-20170020877	01-26-2017	GRIGORIADIS; Dimitri E.	
	018	US-20220143037	05-12-2022	HOWERTON; Alexis et al.	
	019	US-20220211711	07-07-2022	HOWERTON; Alexis et al.	

Examiner Signature	/SARAH PIHONAK/	Date Considered	05/07/2025

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FOREIGN PATENT DOCUMENTS

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	001	CN-101516887-A	08-26-2009	LILLY CO ELI [US]	Abstract:	☒
	002	CN-106102740-A	11-09-2016	NEUROCRINE BIOSCIENCES INC.	Abstract:	☒
	003	JP-2010504344-A	02-12-2010	ELI LILLY AND CO.	Machine Translation:	☒
	004	JP-2017503030-A	01-26-2017	NEUROCRINE BIOSCIENCES, INC.	Machine Translation:	☒
	005	JP-H0971528-A	03-18-1997	HAYASHIBARA BIOCHEM LAB [JP]	Abstract:	☒
	006	WO-0040529-A1	07-13-2000	ANGIOGENE PHARM LTD [GB], et al.		☐
	007	WO-0041669-A2	07-20-2000	ANGIOGENE PHARM LTD [GB], et al.		☐
	008	WO-0192224-A1	12-06-2001	ASTRAZENECA AB [SE], et al.		☐
	009	WO-0204434-A1	01-17-2002	ANGIOGENE PHARM LTD [GB], et al.		☐
	010	WO-0208213-A1	01-31-2002	ANGIOGENE PHARM LTD [GB], et al.		☐

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				Examiner Name	Not Yet Assigned
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	011	WO-2007109853-A1	10-04-2007	VELACOR THERAPEUTICS PTY LTD [AU], et al.		☐
	012	WO-2008036579-A1	03-27-2008	LILLY CO ELI [US], et al.		☐
	013	WO-2015112642-A1	07-30-2015	NEUROCRINE BIOSCIENCES INC [US]		☐
	014	WO-2019036472-A1	02-21-2019	SPRUCE BIOSCIENCES INC [US]		☐
	015	WO-2019036503-A1	02-21-2019	SPRUCE BIOSCIENCES INC [US]		☐
	016	WO-2019210266-A1	10-31-2019	SPRUCE BIOSCIENCES INC [US]		☐
	017	WO-9722596-A1	06-26-1997	ZENECA LTD [GB], et al.		☐
	018	WO-9730035-A1	08-21-1997	ZENECA LTD [GB], et al.		☐
	019	WO-9732856-A1	09-12-1997	ZENECA LTD [GB], et al.		☐
	020	WO-9813354-A1	04-02-1998	ZENECA LTD [GB], et al.		☐
	021	WO-9902166-A1	01-21-1999	ANGIOGENE PHARM LTD [GB], et al.		☐

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NON-PATENT LITERATURE DOCUMENTS			
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	001	AL-MUHAMMED, J. et al. In-vivo studies on dexamethasone sodium phosphate liposomes. Journal of microencapsulation 13(3):293-306 (1996).	☐
	002	BERGE, Stephen M. et al. Pharmaceutical Salts. Journal of Pharmaceutical Sciences 66(1):1-19 (1977).	☐
	003	CHEN, Hua-dong. et al. Ovarian adrenal rest tumors undetected by imaging studies and identified at surgery in three females with congenital adrenal hyperplasia unresponsive to increased hormone therapy dosage. Endocrine pathology 28(2):146-151 (2017).	☐
	004	CHONN, Archadio et al. Recent Advances in Liposomal Drug-delivery Systems. Current Opinion in Biotechnology 6(6):698-708 (1995).	☐
	005	Co-pending U.S. Application No. 18/941,832, inventors HOWERTON; Alexis et al., filed on November 08, 2024.	☐
	006	Co-pending U.S. Application No. 19/043,264, inventors HOWERTON; Alexis et al., filed on January 31, 2025.	☐
	007	Co-pending U.S. Application No. 19/043,275, inventors HOWERTON; Alexis et al., filed on January 31, 2025.	☐
	008	EYLES et al. Oral delivery and fate of poly(lactic acid) microsphere-encapsulated interferon in rats. J Pharm Pharmacol. 49(7):669-74 (1997).	☐
	009	GAO, Zhi-Hui. et al. Controlled Release of a Contraceptive Steroid From Biodegradable and Injectable Gel Formulations: in Vitro Evaluation. Pharmaceutical research 12(6):857-863 (1995).	☐
	010	JIN et al. Testicular adrenal rest tumors in a patient with untreated congenital adrenal hyperplasia. Korean J Pediatr 2011;54(3):137-140.	☐

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	011	KAPRARA, et al. The corticotropin releasing factor system in cancer: expression and pathophysiological implications. Cellular and molecular life sciences 67(8):1293-1306 (2010).	☐
	012	MENDES-DOS-SANTOS et al. Prevalence of Testicular Adrenal Rest Tumor and Factors Associated with Its Development in Congenital Adrenal Hyperplasia. Hormone Res. In Paed. 90:161-168 (2018).	☐
	013	MUNSON, Peter et al. Ligand: a Versatile Computerized Approach for Characterization of Ligand-binding Systems. Analytical Biochemistry 107(1):220-239 (1980).	☐
	014	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Granting Institution of Post-Grant Review of U.S. Patent No. 11,007,201 dated December 1, 2023 (pp. 1-38) (PGR2022-00025).	☐
	015	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Final Written Decision of Post-Grant Review of U.S. Patent No. 10,849,908 dated November 26, 2024 (pp. 1-62) (PGR2021-00088).	☐
	016	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Final Written Decision of Post-Grant Review of U.S. Patent No. 11,007,201 dated November 27, 2024 (pp. 1-60) (PGR2022-00025).	☐
	017	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 10,849,908 dated May 28, 2021 (pp. 1-90) (PGR2021-00088).	☐
	018	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Petition for Post Grant Review of U.S. Patent No. 11,007,201 dated February 18, 2022 (pp 1-92) (PGR2022-00025).	☐

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	019	OSTRO, Mark J. et al. Use of Liposomes as Injectable-drug Delivery Systems. American Journal of Hospital Pharmacy 46(8):1576-1587 (1989).	☐
	020	PCT/US2019/029486 International Invitation to Pay Additional Fees dated June 4, 2019.	☐
	021	PCT/US2019/029486 International Search Report and Written Opinion dated August 12, 2019.	☐
	022	RAO. Recent developments of collagen-based materials for medical applications and drug delivery systems. J Biomater Sci Polym Ed. 7(7):623-45 (1995).	☐
	023	REICHMAN et al. Fertility in Patients with Congenital Adrenal Hyperplasia. Fertility and Sterility, Vol. 101, No. 2, 2014. 301-309.	☐
	024	REISCH et al. Testicular adrenal rest tumors develop independently of long-term disease control: a longitudinal analysis of 50 adult men with congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency. J. Clin. Endocrinol. Metab. 98(11):E1820-E1826 (2013).	☐
	025	SMEETS et. al. Molecular characterization of testicular adrenal rest tumors in congenital adrenal hyperplasia: lesions with both adrenocortical and Leydig cell features. JCEM 100(3):E524-E530 (2015).	☐
	026	TIOSANO et al. Ovarian adrenal rest tumor in a congenital adrenal hyperplasia patient with adrenocorticotropin hypersecretion following adrenalectomy. Hormone Res. in Paediatrics 74:223-228 (2010).	☐
	027	U.S. Serial No. 17/081,694 Office Action dated February 26, 2021.	☐
	028	U.S. Serial No. 17/081,694 Office Action dated June 11, 2021.	☐
	029	U.S. Serial No. 17/667,285 Office Action dated December 29, 2023.	☐

Examiner Signature	/SARAH PIHONAK/	Date Considered	05/07/2025

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. Applicant's unique citation designation number (optional). See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	7	of	9	Attorney Docket Number	50535-710.305

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	030	U.S. Serial No. 17/667,285 Office Action dated June 10, 2024.	☐
	031	ZAAROUR et al. Bilateral Ovary Adrenal Rest Tumor in a Congenital Adrenal Hyperplasia Following Adrenalectomy. Endocrinol. Pract. 20(4):e69-e74 (2014).	☐

Examiner Signature	/SARAH PIHONAK/	Date Considered	05/07/2025

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. Applicant's unique citation designation number (optional). See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	
				Examiner Name	Not Yet Assigned
Sheet	8	of	9	Attorney Docket Number	50535-710.305

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☐ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☒ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	**/Victoria Cheng/**	Date (YYYY-MM-DD)	**2025-02-05**
Name/Print	Victoria Cheng	Registration Number	79641

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Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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BIB DATA SHEET

CONFIRMATION NO. 1040

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
19/043,303	01/31/2025 RULE	514	1627	50535-710.305

APPLICANTS
Spruce Biosciences, Inc., South San Francisco, CA;

INVENTORS
Alexis HOWERTON, San Francisco, CA;
Hal GERBER, San Francisco, CA;

**** CONTINUING DATA ***************************
This application is a CON of 18/941,832 11/08/2024
which is a CON of 17/667,285 02/08/2022 ABN
which is a CON of 17/081,694 10/27/2020 PAT 11304950
which is a CON of PCT/US2019/029486 04/26/2019
which claims benefit of 62/822,815 03/23/2019
and claims benefit of 62/663,951 04/27/2018

**** FOREIGN APPLICATIONS **************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
03/10/2025

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
❑ Yes ☑ No	❑ Yes ☑ No	/SARAH PIHONAK/ Examiner's Signature	❑ SP Initials	CA	14	19	1

ADDRESS
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050
UNITED STATES

TITLE
METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

FILING FEE RECEIVED	FEES: Authority has been given in Paper
0.00	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:

❑ All Fees
❑ 1.16 Fees (Filing)
❑ 1.17 Fees (Processing Ext. of time)
❑ 1.18 Fees (Issue)
❑ Other _____
❑ Credit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,303	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**1040**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: October 3, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $280.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.305).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: October 3, 2025

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
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				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	5	Attorney Docket Number	50535-710.305

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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				Examiner Name	PIHONAK, SARAH
Sheet	2	of	5	Attorney Docket Number	50535-710.305

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	BRADLEY, D. Anawalt et al. Chapter 12: Testes. Greenspan's Basic & Clinical Endocrinology. 10th ed. New York: McGraw-Hill Education (pp. 413-442) (2018).	☐
	002	EP3784233 Case Details for ACT_34386/2025 (1 pg) (2025).	☐
	003	FDA Approves New Treatment for Congenital Adrenal Hyperplasia, US Food and Drug Administration, December 13, 2024. Available at URL: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-congenital-adrenal-hyperplasia? pp.1-2.	☐
	004	SPEISER, Phyllis W. et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism 103(11):4043-4088 (2018).	☐
	005	Spruce Power Holding Corporation. Quarterly Report (Form 10-Q) for the period ended June 30, 2024. United States Securities and Exchange Commission, August 13, 2024. Available at: https://www.sec.gov/Archives/edgar/data/1772720/000162828024037238/spru-20240630.htm pp. 1-53.	☐
	006	U.S. Serial No. 19/043,264 Office Action dated August 18, 2025.	☐
	007	U.S. Serial No. 19/043,275 Office Action dated September 12, 2025.	☐
	008	World Health Organization. Drug Information 33(1):122 (2019).	☐

EXAMINER SIGNATURE			
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				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	3	of	5	Attorney Docket Number	50535-710.305

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Kaia R. Parenti/	Date (YYYY-MM-DD)	2025-10-03
Name/Print	Kaia R. Parenti	Registration Number	81050

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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				Complete if Known	
Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	4	of	5	Attorney Docket Number	50535-710.305

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,303	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**1040**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: October 3, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $280.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.305).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: October 3, 2025

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	5	Attorney Docket Number	50535-710.305

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	2	of	5	Attorney Docket Number	50535-710.305

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	BRADLEY, D. Anawalt et al. Chapter 12: Testes. Greenspan's Basic & Clinical Endocrinology. 10th ed. New York: McGraw-Hill Education (pp. 413-442) (2018).	☐
	002	EP3784233 Case Details for ACT_34386/2025 (1 pg) (2025).	☐
	003	FDA Approves New Treatment for Congenital Adrenal Hyperplasia, US Food and Drug Administration, December 13, 2024. Available at URL: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-congenital-adrenal-hyperplasia? pp.1-2.	☐
	004	SPEISER, Phyllis W. et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism 103(11):4043-4088 (2018).	☐
	005	Spruce Power Holding Corporation. Quarterly Report (Form 10-Q) for the period ended June 30, 2024. United States Securities and Exchange Commission, August 13, 2024. Available at: https://www.sec.gov/Archives/edgar/data/1772720/000162828024037238/spru-20240630.htm pp. 1-53.	☐
	006	U.S. Serial No. 19/043,264 Office Action dated August 18, 2025.	☐
	007	U.S. Serial No. 19/043,275 Office Action dated September 12, 2025.	☐
	008	World Health Organization. Drug Information 33(1):122 (2019).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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Sheet	3	of	5	Attorney Docket Number	50535-710.305

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☐ See attached timing statement under 37 CFR 1.97(e).

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TIMING FEE

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Signature:	/Kaia R. Parenti/	Date (YYYY-MM-DD)	2025-10-03
Name/Print	Kaia R. Parenti	Registration Number	81050

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Doc description: Information Disclosure Statement (IDS) Filed

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UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,303	**10/03/2025 04:09:49 PM Z ET**	**50535-710.305**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1040	FILED BY	JENNIFER VAIL
PATENT CENTER #	72578916	AUTHORIZED BY	Kaia Parenti
CUSTOMER #	21971	FILING DATE	01/31/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 232415	**E202503G10156402**	**JENNIFER VAIL**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	280.00	1	280.00
			TOTAL AMOUNT:	**¤280.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,303	**10/03/2025 04:09:49 PM Z ET**	**50535-710.305**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1040	FILED BY	JENNIFER VAIL
PATENT CENTER #	72578916	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kaia Parenti

Documents

TOTAL DOCUMENTS: 10

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Spruce_50535-710-305_sIDS.pdf		9	-	290 KB
Spruce_50535-710-305_sIDS-TRAN.LET.pdf	(1-4)	4	Transmittal Letter	154 KB
Spruce_50535-710-305_sIDS-IDS.pdf	(5-9)	5	Information Disclosure Statement (IDS) Form (SB08)	131 KB
NPL_EP3784233_CaseDetails_2025.pdf		1	Non Patent Literature	66 KB
NPL_US19043275_OA_2025_09_12.pdf		8	Non Patent Literature	223 KB
NPL_World_Drug_Information_122_2019.pdf		1	Non Patent Literature	499 KB

NPL_US19043264_OA_2025_08_18.pdf	14	Non Patent Literature	469 KB
NPL_FDA_Congenital_Adrenal_Hyperplasia_2024.pdf	2	Non Patent Literature	760 KB
NPL_Bradley_Chapter_12_Testes_413-442.pdf	55	Non Patent Literature	1508 KB
NPL_Spruce_Quarterly_Report_2024.pdf	53	Non Patent Literature	16322 KB
NPL_SPEISER_Congenital_adrenal_4043_4088.pdf	46	Non Patent Literature	22285 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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NPL_FDA_Congenital_Adrenal_Hyperplasia_2024.pdf	8010561785130E9DB463761F495158C13AF22035FC8EC019F7B8580D1E6763B4A47D0E0EAFC5DB796A7DA05312E3A0AAA94F495AA75B1B046EB4BEFC146F8998
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es_413-442.pdf	D8DD7A55CEA44C22B5C57D660C670754EF7D97B81BC911BF01CF1B3B10EA60B0814F42C0392FEAE
NPL_Spruce_Quarterly_Report_2024.pdf	CD93E8C17AA4157421D317D10B340427073D4B8619F011C221455D4298240F8C81D40B2CC573059A3B8FB2ED5CB63F832F7F7EB1606051446F85B0934739ED27
NPL_SPEISER_Congenital_adrenal_4043_4088.pdf	7C3A435DC5BED745595FB6B78845BB38694684F0AEEFE1FA32DE9EBB303C94D13D72CCE742D8008AC544E0B2D29D3476D2786141CA7017FEF59C003DE2432E20

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 19/043,303	Filing Date 01/31/2025	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $200 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $600 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	11/13/2025	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 19	Minus	** 20	= 0		x $200 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $600 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	Examiner
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/YEN NGO/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,303	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**1040**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: November 14, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.305).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: November 14, 2025

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	7	Attorney Docket Number	50535-710.305

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,303
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				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	2	of	7	Attorney Docket Number	50535-710.305

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	001	ÇAKIR et al., Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia. J Clin Res Pediatr Endocrinol 4(2):94-100 (2012).	☐
	002	BACON et al., Effect of Cortisol Treatment on Hormonal Relationships in Congenital Adrenal Hyperplasia. Clinical Endocrinology 6:113-126 (1977).	☐
	003	BENVENGA et al., Testicular adrenal rests: evidence for luteinizing hormone receptors and for distinct types of testicular nodules differing for their autonomization. European Journal of Endocrinology 141:231-237 (1999).	☐
	004	Chemical Abstracts Service. CAS Registry: 752253-39-7. 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-((1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-2-propyn-1-yl-2-thiazolamine: pp. 1-35. STN Entry Date October 11, 2005. Retrieved October 14, 2025. Retrieved from :https://pubchem.ncbi.nlm.nih.gov/compound/5282340.	☐
	005	CLAAHSEN et al., Testicular Tumors in Patients with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency Show Functional Features of Adrenocortical Tissue. J Clin Endocrinol Metab. 92(9):3674-80 (2007).	☐
	006	GUPTA et al., Corticosteroid Physiology and Principles of Therapy. Indian J Pediatr 75(10):1039-1044 (2008).	☐
	007	GWATHMEY et al., Glucocorticoid-Induced Fetal Programming Alters the Functional Complement of Angiotensin Receptor Subtypes Within the Kidney. Hypertension 57(3):620-6 (2011).	☐
	008	HINDMARSH et al., Congenital Adrenal Hyperplasia A Comprehensive Guide. Elsevier, ISBN: 978-0-12-811483-4 (pp. 263-264 and 319-320) (2017).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

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				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	3	of	7	Attorney Docket Number	50535-710.305

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	009	MATSUBARA. Pathophysiological Role of Angiotensin II Type 2 Receptor in Cardiovascular and Renal Diseases. Circ Res. 83:1182-1191 (1998).	☐
	010	MESA et al., Immunophenotypic differences between neoplastic and non-neoplastic androgen-producing cells containing and lacking Reinke crystals. Virchows Arch. 469(6):679-686 (2016).	☐
	011	MORRIS, David. Steroid-induced Diabetes and Hyperglycaemia. Part 1: Mechanisms and Risks. Diabetes & Primary Care 20(4):151-153 (2018).	☐
	012	NAGURNEY et al., The Accuracy and completeness of Data Collected by Prospective and Retrospective Methods. ACAD EMERG MED 12(9):884-95 (September 2005).	☐
	013	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Denying Institution of Inter Partes Review in U.S. Patent No. 12,115,166 dated October 03, 2025 (pp 1-3) (PGR-2025-00032).	☐
	014	NEWFIELD, Ron S. et al. Crinecerfont, a CRF1 Receptor Antagonist, Lowers Adrenal Androgens in Adolescents with Congenital Adrenal Hyperplasia. The Journal of Clinical Endocrinology & Metabolism 108(11):2871-2878 (2023).	☐
	015	POYRAZOGLU et al., Prevalence of testicular microlithiasis in males with congenital adrenal hyperplasia and its association with testicular adrenal rest tumors. Horm Res Paediatr. 73:443-448 (2010).	☐
	016	Regulation (EC) No 141/2000 Of the European Parliament and of the Council of 16 December 1999 on orphan medical products (pp. 1-5).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant

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				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	4	of	7	Attorney Docket Number	50535-710.305

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	017	SOWERS et al., Effect of dexamethasone on gonadotropin responsiveness to luteinizing hormone-releasing hormone and clomiphene in women with secondary amenorrhea. Am J Obstet Gynecol. 134(3):325-8 (1979 Jun 1).	☐
	018	SPIERLING, Samantha R, and Eric P Zorrilla. et al. Don't stress about CRF: Assessing the translational failures of CRF1 antagonists. Psychopharmacology 234(9-10):1467-1481 (2017).	☐
	019	U.S. Serial No. 17/578,149 Office Action dated October 6, 2025.	☐
	020	U.S. Serial No. 18/438,060 Office Action dated October 7, 2025.	☐
	021	XAVIER et al., Gene Expression Control by Glucocorticoid Receptors during Innate Immune Responses. Front. Endocrinol. 7:31 (2016).	☐
	022	XUE et al. Glucocorticoid Modulates Angiotensin II Receptor Expression Patterns and Protects the Heart from Ischemia and Reperfusion Injury. PLoS One 9(9):e106827 (2014).	☐

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	5	of	7	Attorney Docket Number	50535-710.305

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Kaia R. Parenti/	Date (YYYY-MM-DD)	2025-11-14
Name/Print	Kaia R. Parenti	Registration Number	81050

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	HOWERTON; Alexis et al.	Group Art Unit:	1627
Serial Number:	19/043,303	Examiner:	PIHONAK, SARAH
Filing or 371 (c) Date:	2025-01-31	**CONFIRMATION NO:**	**1040**
Title:	METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS		

FILED ELECTRONICALLY ON: November 14, 2025

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of [$280.00/112.00/56.00] as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of [$280.00/112.00/56.00] as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay. The Patent Term Adjustment Statement Under 37 CFR 1.704(d) on Form PTO/SB/133 is filed herewith.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non-Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $280.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 50535-710.305).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: November 14, 2025

By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81050

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	1	of	7	Attorney Docket Number	50535-710.305

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	001	ÇAKIR et al., Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia. J Clin Res Pediatr Endocrinol 4(2):94-100 (2012).	☐
	002	BACON et al., Effect of Cortisol Treatment on Hormonal Relationships in Congenital Adrenal Hyperplasia. Clinical Endocrinology 6:113-126 (1977).	☐
	003	BENVENGA et al., Testicular adrenal rests: evidence for luteinizing hormone receptors and for distinct types of testicular nodules differing for their autonomization. European Journal of Endocrinology 141:231-237 (1999).	☐
	004	Chemical Abstracts Service. CAS Registry: 752253-39-7. 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-((1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-N-2-propyn-1-yl-2-thiazolamine: pp. 1-35. STN Entry Date October 11, 2005. Retrieved October 14, 2025. Retrieved from :https://pubchem.ncbi.nlm.nih.gov/compound/5282340.	☐
	005	CLAAHSEN et al., Testicular Tumors in Patients with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency Show Functional Features of Adrenocortical Tissue. J Clin Endocrinol Metab. 92(9):3674-80 (2007).	☐
	006	GUPTA et al., Corticosteroid Physiology and Principles of Therapy. Indian J Pediatr 75(10):1039-1044 (2008).	☐
	007	GWATHMEY et al., Glucocorticoid-Induced Fetal Programming Alters the Functional Complement of Angiotensin Receptor Subtypes Within the Kidney. Hypertension 57(3):620-6 (2011).	☐
	008	HINDMARSH et al., Congenital Adrenal Hyperplasia A Comprehensive Guide. Elsevier, ISBN: 978-0-12-811483-4 (pp. 263-264 and 319-320) (2017).	☐

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	009	MATSUBARA. Pathophysiological Role of Angiotensin II Type 2 Receptor in Cardiovascular and Renal Diseases. Circ Res. 83:1182-1191 (1998).	☐
	010	MESA et al., Immunophenotypic differences between neoplastic and non-neoplastic androgen-producing cells containing and lacking Reinke crystals. Virchows Arch. 469(6):679-686 (2016).	☐
	011	MORRIS, David. Steroid-induced Diabetes and Hyperglycaemia. Part 1: Mechanisms and Risks. Diabetes & Primary Care 20(4):151-153 (2018).	☐
	012	NAGURNEY et al., The Accuracy and completeness of Data Collected by Prospective and Retrospective Methods. ACAD EMERG MED 12(9):884-95 (September 2005).	☐
	013	Neurocrine Biosciences, Inc. (Petitioner) v. Spruce Biosciences, Inc. (Patent Owner). Decision Denying Institution of Inter Partes Review in U.S. Patent No. 12,115,166 dated October 03, 2025 (pp 1-3) (PGR-2025-00032).	☐
	014	NEWFIELD, Ron S. et al. Crinecerfont, a CRF1 Receptor Antagonist, Lowers Adrenal Androgens in Adolescents with Congenital Adrenal Hyperplasia. The Journal of Clinical Endocrinology & Metabolism 108(11):2871-2878 (2023).	☐
	015	POYRAZOGLU et al., Prevalence of testicular microlithiasis in males with congenital adrenal hyperplasia and its association with testicular adrenal rest tumors. Horm Res Paediatr. 73:443-448 (2010).	☐
	016	Regulation (EC) No 141/2000 Of the European Parliament and of the Council of 16 December 1999 on orphan medical products (pp. 1-5).	☐

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	018	SPIERLING, Samantha R, and Eric P Zorrilla. et al. Don't stress about CRF: Assessing the translational failures of CRF1 antagonists. Psychopharmacology 234(9-10):1467-1481 (2017).	☐
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Sheet	5	of	7	Attorney Docket Number	50535-710.305

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☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached timing statement under 37 CFR 1.97(e).

☒ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and attached instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☒ No IDS size fee is required under 37 CFR 1.17 (v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 11.18. Please see CFR 1.4(d) for the form of the signature.

Signature:	/Kaia R. Parenti/	Date (YYYY-MM-DD)	2025-11-14
Name/Print	Kaia R. Parenti	Registration Number	81050

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)				Complete if Known	
				Application Number	19/043,303
				Filing Date	01-31-2025
				First Named Inventor	HOWERTON; Alexis
				Art Unit	1627
				Examiner Name	PIHONAK, SARAH
Sheet	6	of	7	Attorney Docket Number	50535-710.305

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,303	**11/14/2025 01:36:17 PM Z ET**	**50535-710.305**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1040	FILED BY	JENNIFER VAIL
PATENT CENTER #	73185799	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kaia Parenti

Documents

TOTAL DOCUMENTS: 24

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Spruce 50535-710_305_IDS.pdf		11	-	308 KB
Spruce 50535-710_305_IDS-TRAN.LET.pdf	(1-4)	4	Transmittal Letter	155 KB
Spruce 50535-710_305_IDS-IDS.pdf	(5-11)	7	Information Disclosure Statement (IDS) Form (SB08)	148 KB
NPL_013_NEUROCRIN_V_SPRUCE_Decision_Denying_Interpartes_03Oct2025.pdf		3	Non Patent Literature	61 KB
NPL_016_Regulation_EC_No_141-2000.pdf		5	Non Patent Literature	79 KB
NPL_011_MORRIS_Steroid_		3	Non Patent Literature	351 KB

Diabetes_151_153_2018.pdf			
NPL_012_NAGURNEY_TheAccuracyandcompleteness_884-95.pdf	12	Non Patent Literature	264 KB
NPL_017_SOWERS_Effectofdexamethasone_325-8.pdf	4	Non Patent Literature	422 KB
NPL_020_US18438060_OA_2025_10_07.pdf	21	Non Patent Literature	850 KB
NPL_014_NEWFIELD_Crinecerfont_CRF1_2871_2878_2023.pdf	8	Non Patent Literature	851 KB
NPL_019_US17578149_OA_2025_10_06.pdf	30	Non Patent Literature	1228 KB
NPL_008_HINDMARSH_CongenitalAdrenalHyperplasia_pages_263-264_and_319-320.pdf	7	Non Patent Literature	1451 KB
NPL_002_BACON_EffectofCortisolTreatment_113-126.pdf	14	Non Patent Literature	1547 KB
NPL_018_SPIERLING_CRF_Assessings_1467_1481_2017.pdf	15	Non Patent Literature	2033 KB
NPL_001_CAKIR_TesticularAdrenalRest_94-100.pdf	7	Non Patent Literature	2239 KB
NPL_003_BENVENGA_Testicularadrenalrests_231-237.pdf	7	Non Patent Literature	3150 KB
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NPL_015_POYRAZOGLU_Prevalenceoftesticular_443-448.pdf	6	Non Patent Literature	3220 KB
NPL_007_GWATHMEY_GlucocorticoidInducedFetal_620-6.pdf	7	Non Patent Literature	4598 KB
NPL_004_CAS_752253-39-7.pdf	35	Non Patent Literature	4567 KB
NPL_005_CLAAHSEN_Testi	7	Non Patent Literature	5481 KB

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NPL_022_XUE_GlucocorticoidModulatesAngiotensin_e106827.pdf	10	Non Patent Literature	5568 KB
NPL_010_MESA_Immunophenotypicdifferencesbetween_679-686.pdf	9	Non Patent Literature	6916 KB
NPL_021_XAVIER_GeneExpressionControl_31.pdf	8	Non Patent Literature	6068 KB
NPL_009_MATSUBARA_PathophysiologicalRoleof_1182-1191.pdf	10	Non Patent Literature	10855 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,303	**11/14/2025 01:36:17 PM Z ET**	**50535-710.305**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1040	FILED BY	JENNIFER VAIL
PATENT CENTER #	73185799	AUTHORIZED BY	Kaia Parenti
CUSTOMER #	21971	FILING DATE	01/31/2025
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Alexis HOWERTON

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 232415	**E2025ADD36426906**	**JENNIFER VAIL**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	280.00	1	280.00
			TOTAL AMOUNT:	**$280.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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PATENT
Attorney Docket No. 50535-710.305

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Alexis Howerton et al. Application No.: 19/043,303 Filing Date: January 31, 2025 Title: METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS	Confirmation No.: 1040 Art Unit: 1627 Examiner: Pihonak, Sarah Customer No.: 21971 Certificate of Electronic Filing I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office's electronic filing system to the USPTO on November 13, 2025. By: Colleen Mensching Colleen Mensching

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Dear Commissioner:

In response to the Non-Final Office Action mailed September 5, 2025, setting an initial due date of December 5, 2025, Applicant respectfully requests reconsideration of the above-referenced application in view of the following amendments and remarks.

Amendments to the Specification begin on page **2** of this paper.
Amendments to the Claims begin on page **3** of this paper.
Remarks begin on page **7** of this paper.
Conclusion begins on page **8** of this paper.

AMENDMENTS TO THE SPECIFICATION

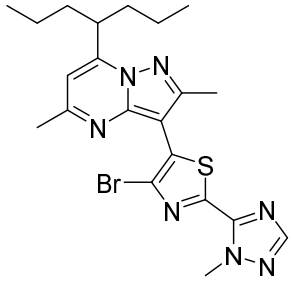
Applicant provides herewith both a clean copy and a marked copy of a substitute specification, excluding claims, in compliance with 37 C.F.R. § § 1.52, 1.121, and 1.125. The amendments follow the Certification of Correction corresponding to US Pat. No. 11,304,950, which was submitted on March 12, 2025 and accepted on June 17, 2025.

Applicant respectfully requests that the specification of record be replaced with the substitute specification filed herewith.

AMENDMENTS TO THE CLAIMS

Listing of the Claims

1. (**Currently Amended**) A method of changing a metabolic parameter of a subject having a testicular adrenal rest tumor (TART) or an ovarian adrenal rest tumor (OART), comprising administering to the subject in need thereof a small molecule corticotropin-releasing factor type-1 (CRF_1) antagonist, or a pharmaceutically acceptable salt thereof, wherein the small molecule CRF_1 antagonist is: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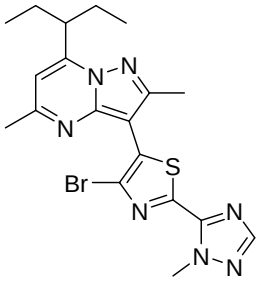
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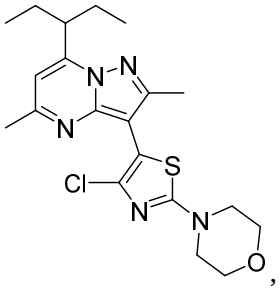
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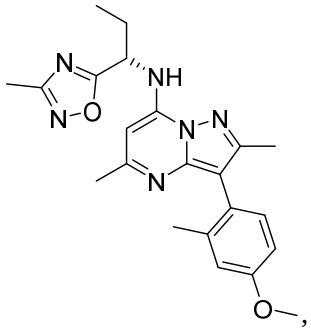
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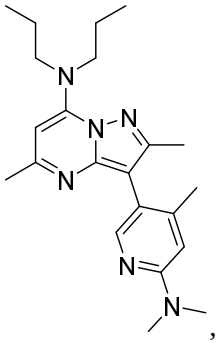
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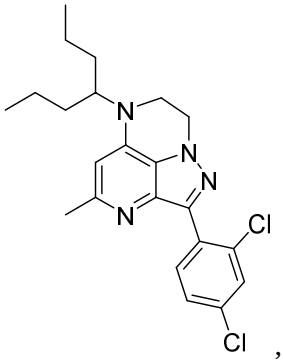
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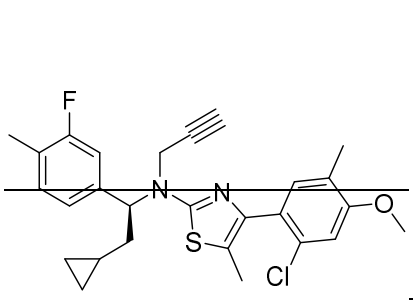
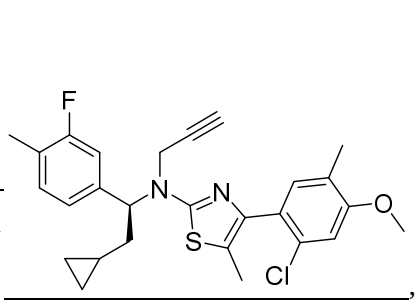
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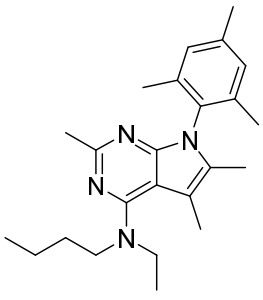
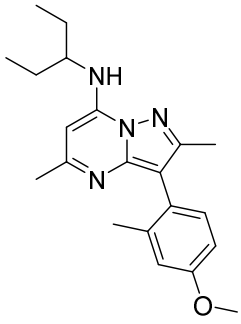
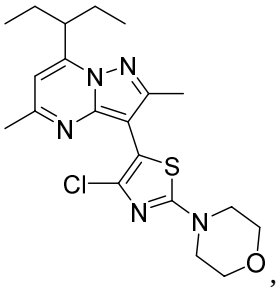




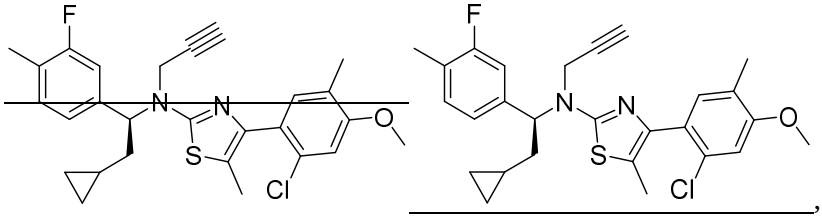
, or , or a pharmaceutically acceptable salt thereof, and wherein the metabolic parameter comprises fasting glucose, HbA1c level, insulin sensitivity, or a lipid profile, or a combination thereof.

2. (**Previously Presented**) The method of claim 1, wherein the small molecule CRF_1 antagonist is:



, or a pharmaceutically acceptable salt thereof.

3. (**Currently Amended**) The method of claim 1, wherein the small molecule CRF_1 antagonist is:



, or a pharmaceutically acceptable salt thereof.

4. (**Previously Presented**) The method of claim 1, wherein the metabolic parameter is insulin sensitivity.

5. (**Previously Presented**) The method of claim 1, wherein the subject has congenital adrenal hyperplasia (CAH).

6. (**Previously Presented**) The method of claim 1, wherein the administering reduces a size of the TART or the OART.
7. (**Previously Presented**) The method of claim 1, wherein the administering reduces a number of the TART or the OART.
8. (**Previously Presented**) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered at a dose of about 10 mg/day to about 400 mg/day to the subject.
9. (**Previously Presented**) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 50 mg.
10. (**Previously Presented**) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 100 mg.
11. (**Previously Presented**) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 200 mg.
12. (**Previously Presented**) The method of claim 8, wherein the small molecule CRF_1 antagonist is administered at a dose of about 400 mg.
13. (**Previously Presented**) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered to the subject once per day.
14. (**Previously Presented**) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered to the subject twice per day.
15. (**Previously Presented**) The method of claim 1, wherein the small molecule CRF_1 antagonist is administered orally.
16. (**Previously Presented**) The method of claim 1, wherein the small molecule CRF_1 antagonist is formulated as a capsule or tablet.
17. (**Previously Presented**) The method of claim 1, wherein the administering reduces a plasma concentration of a biomarker comprising 17α-hydroxyprogesterone (17-OHP), adrenocorticotropic hormone (ACTH), testosterone, androstenedione (A4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone-binding globulin (SHBG), renin, or aldosterone, or a combination thereof.
18. (**Currently Amended**) The method of ~~claim 1~~ claim 17, wherein the biomarker is selected from the group consisting of 17-OHP, ACTH, and A4.

19. (**Currently Amended**) The method of ~~claim 1~~ claim 17, wherein the plasma concentration of the biomarker is at least 10% from baseline.

REMARKS

Claims 1-19 were pending prior to entry of the amendments presented in this response. Claims 1, 3, 18, and 19 are herein amended, support for which can be found in the as-filed application. No new matter is added by any of these amendments. Reconsideration and allowance are respectfully requested based on the amendments and following remarks.

Indefiniteness under 35 U.S.C. §112

Claims 18 and 19 are rejected under 35 U.S.C. §112(b) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor regards as the invention. Without conceding to the basis of the rejection, Applicant herein amends claims 18 and 19 to depend from claim 17. Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112(b).

Double Patenting

Claims 1-19 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 and 19 of U.S. Patent No. 11,304,950 B2.

Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 72-83 and 85-91 of copending Application No. 18941832.

Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 and 17-21 of copending Application No. 19043264 in view of Stikkelbroeck et. al., Fertility & Sterility, vol. 80(4), pp. 1030-1036, publ. 2003.

Without acquiescing to the basis of the rejection and for the purpose of compact prosecution, Applicant files herein a terminal disclaimer over U.S. Patent No. 11,304,950, U.S. Application No. 18/941,832, and U.S. Application No. 19/043,264. Therefore, Applicant respectfully requests withdrawal of the rejections above and allowance of the pending claims.

Claim Objection

Claims 1 and 3 are objected to because of the presence of a functional group indicating a carbon atom with 5 bonds. Applicant herein amends claims 1 and 3 to correct the structure.

CONCLUSION

In light of the remarks set forth above, Applicant believes that the pending claims are under condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned at (212) 453-2852.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit account No. 23-2415 (Attorney Docket No. 50535-710.305).

Respectfully submitted,

Date: November 13, 2025 By: /Kaia R. Parenti/
Kaia R. Parenti, Reg. No. 81,050

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Phone: (650) 493-9300
Customer No. 21971

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

CROSS-REFERENCE

[0001] This application is a continuation of U.S. Application No. 18/941,832, filed November 8, 2024, which is a continuation of U.S. Application No. 17/667,285, filed on February 8, 2022, which is a continuation of U.S. Application No. 17/081,694 filed on October 27, 2020, which issued as U.S. Pat. No. 11,304,950 on April 19, 2022, and which is a continuation of International Application No. PCT/US2019/029486 filed on April 26, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed April 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019, each of which is entirely incorporated herein by reference.

BACKGROUND

[0002] Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

[0003] CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

[0004] Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, *inter alia*, are solutions to these and other problems in the art.

SUMMARY

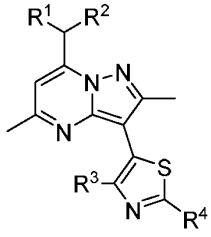
[0005] Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

[0006] Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

[0007] One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

[0008] In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

[0009] One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):

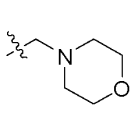


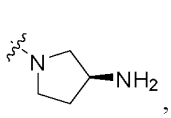
(I), or a pharmaceutically acceptable salt thereof,

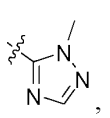
wherein:

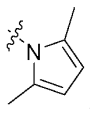
R^1 and R^2 are independently ethyl or n-propyl;

R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl, 

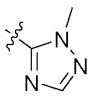
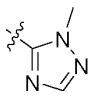
, 

, 

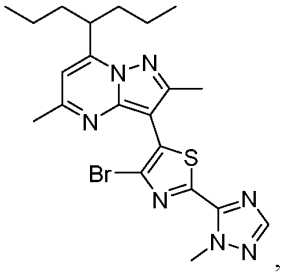
, or 

;

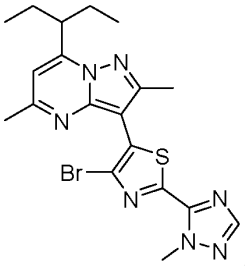
R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0010] In some embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl. In some embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is morpholin-4-yl or  .

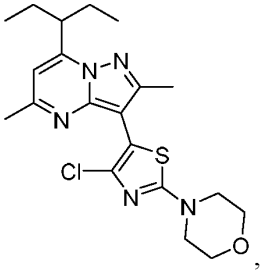
[0011] In some embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl. In some embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0012] In some embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0013] In some embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0014] In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

[0015] In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically

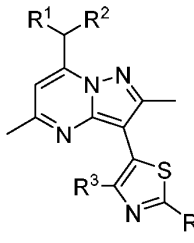
acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0016] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

[0017] In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

[0018] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

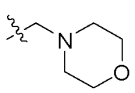
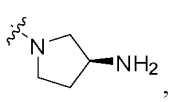
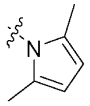
[0019] One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:


(I), or a pharmaceutically acceptable salt thereof,

wherein:

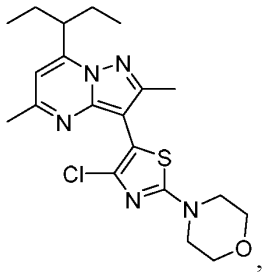
R^1 and R^2 are independently ethyl or n-propyl;

R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  , , or  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0020] In some embodiments, the compound of Formula (I) has the structure:


, or a pharmaceutically acceptable salt thereof.

[0021] In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0022] In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about

265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

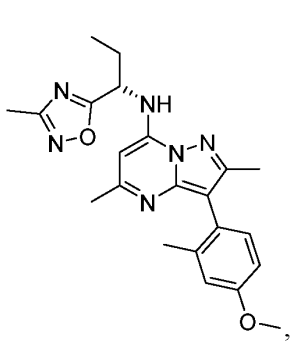
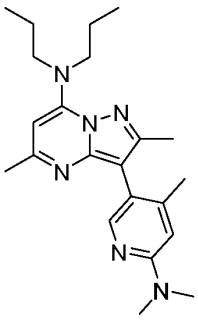
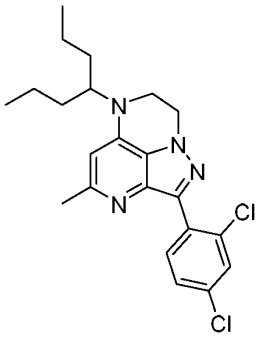
[0023] In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0024] In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

[0025] In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

[0026] In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

[0027] In some embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In some embodiments, the CRF_1 antagonist is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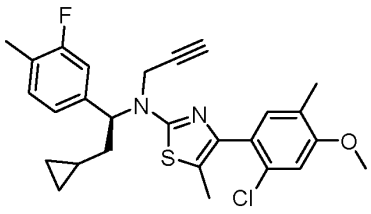
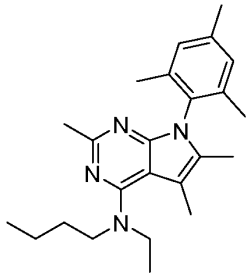
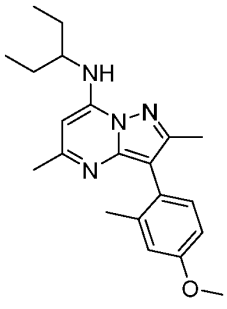
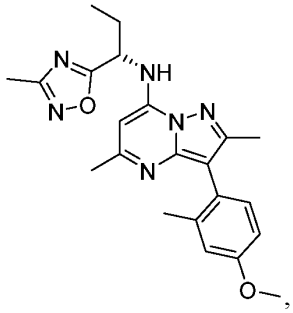



, or a pharmaceutically acceptable salt thereof.

[0028] In some embodiments, the CRF_1 antagonist is


, or a pharmaceutically acceptable salt thereof.

[0029] In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

[0030] In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

[0031] In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with

administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0032] In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0033] In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0034] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0035] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

[0037] FIG. 1A-1B. A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics **(A).** A schematic representation of inhibition of CRF_1 with a CRF_1 antagonist (Compound 1) **(B)**.

[0038] FIG. 2. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

[0039] FIG. 3. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

[0040] FIG. 4. Graphic representation of patient-level response (measuring ACTH levels) to a CRF_1 antagonist (Compound 1).

[0041] FIG. 5A-5B. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a CRF_1 antagonist [Patient 10 **(A)**; Patient 8 **(B)**].

[0042] FIG. 6. Graphic representation of patient-level response (measuring 17-OHP levels) to a CRF_1 antagonist (Compound 1).

[0043] FIG. 7A-7B. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to a CRF_1 antagonist [Patient 10 **(A)**; Patient 8 **(B)**].

[0044] FIG. 8. Graphic representation of patient-level response (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1).

[0045] FIG. 9A-9B. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1) [Patient 10 **(A)**; Patient 8 **(B)**].

[0046] FIG. 10A-10B. Images of a patient with TART pre-treatment with a CRF_1 antagonist (Compound 1) **(A)** and 6-weeks post-treatment with a CRF_1 antagonist (Compound 1) **(B)**.

[0047] FIG. 11A-11B. Graphic representation of an *in vitro* binding assay of a CRF_1 antagonist (Compound 1); ^{125}I-sauvagine binding to rat cerebellar membranes one hour after oral administration of increasing Compound 1 doses **(A)** and *in vivo* inhibition of CRF-induced activity after treatment with a CRF_1 antagonist; Compound 1 (oral, 10 mg/kg) **(B)**.

[0048] FIG. 12A-12B. Graphic representation of ACTH levels (A) and 17-OHP levels (B) after treatment with a CRF_1 antagonist.

[0049] FIG. 13. Graphic representation of hormone responses after treatment with a CRF_1 antagonist (Compound 1).

[0050] FIG. 14 depicts the proof of concept and escalating QD dosing at 10 pm for Cohort A and the single dose level and BID dosing at 10 am and 10 pm for Cohort B.

[0051] FIG. 15A-15D are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

[0052] FIG. 16A-16D are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

[0053] FIG. 17A-17D are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

DETAILED DESCRIPTION

[0054] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

I. Definitions

[0055] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0056] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0057] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

[0058] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms,

with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0059] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

[0060] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0061] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

[0062] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0063] The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0064] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and

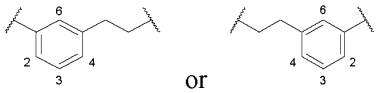
the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

[0065] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0066] The symbol "" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0067] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0068] The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



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[0069] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -CHO, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2CH_3$ $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0070] Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0071] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', $-NR"C(O)_2R'$, -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, $-NR'NR"R"'$, $-ONR'R"$, $-NR'C(O)NR"NR"'R""$, -CN, $-NO_2$, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R"', and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include

groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0072] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', $-NR"C(O)_2R'$, -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, –NR'NR"R"', –ONR'R", –NR'C(O)NR"NR"'R"", -CN, $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R"', and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', and R"" groups when more than one of these groups is present.

[0073] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the

heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0074] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0075] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C''R''R''')_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R'', and R''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0076] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0077] A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

[0078] A “size-limited substituent” or “ size-limited substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0079] A “lower substituent” or “ lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each

substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0080] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0081] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0082] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some

embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0083] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0084] As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0085] The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0086] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0087] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0088] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a

deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0089] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0090] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0091] "Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0092] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0093] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R^{13} substituents are present, each R^{13} substituent may be distinguished as R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc., wherein each of R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc. is defined within the scope of the definition of R^{13} and optionally differently.

[0094] A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

[0095] Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0096] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic,

methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0097] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0098] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

[0099] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0100] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In

general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0101] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of a compound to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0102] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0103] A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

[0104] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and "protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and

homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

[0105] A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, *e.g.*, in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

[0106] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

[0107] The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

[0108] As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

[0109] The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist. In embodiments, an agonist is a molecule that interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

[0110] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

[0111] The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

[0112] The terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms include any recombinant or naturally-occurring form of CRF_1 variants thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of CRF_1 variants (e.g., frameshift mutations) thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF_1). In

embodiments, the CRF_1 protein encoded by the *CRHR1* gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

[0113] The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.*).

[0114] The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

[0115] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer,

premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[0116] The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

[0117] "Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

[0118] "Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

[0119] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic

leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

[0120] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

[0121] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

[0122] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma,

comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

[0123] The terms “treating” or “treatment” refer to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term “treating” and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

[0124] “Treating” or “treatment” as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject’s condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent

of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease's transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (*e.g.*, ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

[0125] "Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

[0126] The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

[0127] "Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0128] An "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a

"therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see*, *e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a CRF1 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

[0129] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0130] Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based

on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0131] The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

[0132] The terms "QD," "qd," and "q.d." refer to once a day, i.e., a drug or therapeutic agent is administered once a day for the duration of the therapeutic regimen.

[0133] The terms "BD," "bd," and "b.i.d." refer to twice a day, i.e., a drug or therapeutic agent is administered two times a day for the duration of the therapeutic regimen.

[0134] The terms "QID," "qid," and "q.i.d." refer to three times a day, i.e., a drug or therapeutic agent is administered three times a day for the duration of the therapeutic regimen.

[0135] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0136] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.,* a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.,* buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.,* intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is

administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.,* by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

[0137] By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0138] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0139] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

[0140] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

[0141] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. colon cancer), cardiovascular disease, metabolic disease, immune or inflammatory disease or disorder.

[0142] The compounds described herein can be administered to treat a fertility disease or disorder and/or cancer. In this regard, the compounds disclosed herein may be administered

either alone to treat such diseases or disorders or may be co-administered with another therapeutic agent to treat such diseases or disorders.

[0143] The compounds disclosed herein may be co-administered with an agonist or antagonist of CRF_1 function. The compounds described herein can be co-administered with conventional anti-cancer/chemotherapeutic.

[0144] "Anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (*e.g.,* cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (*e.g.,* 5- azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (*e.g.,* vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (*e.g.,* irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.,* doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin,

all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor

inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain

antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including recombinant interleukin II, or rlL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine;

mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-

39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, lnanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, lsoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (*e.g.,* dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (*e.g.,* Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (*e.g.,* anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (*e.g.,* anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (*e.g.,* anti-CD20 monoclonal antibody conjugated to ^{111}In, ^{90}Y, or ^{131}I, *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa ™), erlotinib (Tarceva ™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™),

vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

[0145] "Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

[0146] The compounds disclosed herein may be co-administered with an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin); (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5.alpha.-reductase such as finasteride; (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function); (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoli- n-4-amine (gefitinib, AZD 1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazoli- n-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte

growth factor family; (v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin .alpha.v.beta.3 function or an angiostatin); (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213; (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense; (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

[0147] In embodiments, the compounds disclosed herein can be co-administered with an antibody, such as a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax I1-15) or antibody modulating Ig function such as anti-IgE (for example omalizumab).

[0148] In embodiments, treatment of cancer includes administration of an effective amount of at least two of the following: a CRF1 inhibitor, an inhibitor of the PD-L1/PD-1 pathway, an inhibitor of CTLA-4, an agonistic antibody of CD137 (4-1BB). In some embodiments, the method may comprise the use of two or more combinations.

[0149] In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc, ^{64}Cu, ^{67}Cu, ^{89}Sr, ^{86}Y, ^{87}Y, ^{90}Y, ^{105}Rh, ^{111}Ag, ^{111}In, ^{117m}Sn, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi, optionally conjugated to antibodies directed against tumor antigens.

[0150] In addition, a CRF_1 inhibitor may be combined with the therapeutic administration of immune cells, sometimes referred to as adoptive cell transfer. These cells may be cells from the patient, a genetically related or unrelated donor, they may be genetically modified (e.g. CAR-T cells, NK cells, etc), cell lines, genetically modified cell lines and live or dead versions of the

above. CRF1 inhibitors may also be combined with vaccines of any kind (e.g. protein/peptide, viral, bacterial, cellular) to stimulate immune responses to cancer.

[0151] The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

[0152] The CRF_1 inhibitors/CRF_1 antagonists disclosed herein can be administered by any acceptable route, such oral, intraadiposal, intraarterial, intraarticular, intracranial, intradermal, intralesional, intramusculay, intranasal, intraocularal, intrapericardial, intraperitoneal, intrapleural, intraprostatical, intrarectal, intrathecal, intratracheal, intratumoral, intraumbilical, intravaginal, intravenousl, intravesicullar, intravitreal, liposomal, local, mucosal, parenteral, rectal, subconjunctival, subcutaneous, sublingual, topical, transbuccal, transdermal, vaginal, in cremes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

[0153] The CRF_1 inhibitors/CRF_1 antagonists disclosed herein may be administered once daily until study reached endpoint. The CRF_1 inhibitors/CRF_1 antagonists disclosed herein may be administered at least three times but in some studies four or more times depending on the length of the study and/or the design of the study.

[0154] The methods disclosed herein may be used in combination with additional cancer therapy. In some embodiments, the distinct cancer therapy comprises surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy. In some embodiments, the cancer is a chemotherapy-resistant or radio-resistant cancer.

[0155] A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaroytic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (*e.g.*, spodoptera) and

human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

[0156] "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

[0157] The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. In some embodiments, a CRF1 associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with CRF_1 (e.g. an endocrine disorder, a cancer including but not limited to TART or OART). A CRF_1 modulator is a compound that increases or decreases the activity or function or level of activity or level of function of CRF_1. A modulator may act alone, or it may use a cofactor, e.g., a protein, metal ion, or small molecule. Examples of modulators include small molecule compounds and other bioorganic molecules. Numerous libraries of small molecule compounds (e.g., combinatorial libraries) are commercially available and can serve as a starting point for identifying a modulator. The skilled artisan is able to develop one or more assays (e.g., biochemical or cell-based assays) in which such compound libraries can be screened in order to identify one or more compounds having the desired properties; thereafter, the skilled medicinal chemist is able to optimize such one or more compounds by, for example, synthesizing and evaluating analogs and derivatives thereof. Synthetic and/or molecular modeling studies can also be utilized in the identification of an activator.

[0158] The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms "modulate", "modulation" and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of CRF_1, either directly or indirectly, relative to the absence of the molecule.

[0159] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, an endocrine disorder, a disease associated with CRF_1 activity, a CRF_1 associated disease (e.g., testicular

adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) means that the disease (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, an endocrine disorder associated with CRF_1 activity or function may be an endocrine disorder that results (entirely or partially) from aberrant CRF_1 function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or an endocrine disorder wherein a particular symptom of the disease is caused (entirely or partially) by aberrant CRF_1 activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, an endocrine disorder associated with CRF_1 activity or function or a CRF_1 associated disease (e.g., an endocrine disorder including but not limited to TART or OART), may be treated with a compound described herein (e.g., CRF_1 modulator, CRF_1 inhibitor, or CRF_1 antagonist), in the instance where increased CRF_1 activity or function (e.g. signaling pathway activity) causes the disease (e.g., an endocrine disorder such as TART or OART). For example, an endocrine disorder associated with CRF_1 activity or function or a CRF_1 associated endocrine disorder, may be treated with an CRF_1 modulator or CRF_1 inhibitor, in the instance where increased CRF_1 activity or function (e.g. signaling pathway activity) causes the disease.

[0160] The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

[0161] The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propogated to other signaling pathway components. For example, binding of a CRF_1 with a compound as described herein may reduce the level of a product of the CRF_1 catalyzed reaction or the level of a downstream derivative of the product or binding may reduce the interactions between the CRF_1 or a reaction product and downstream effectors or signaling pathway components (e.g., MAP kinase pathway), resulting in changes in cell growth, proliferation, or survival.

[0162] As used herein, the terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" and all other related art-accepted

terms, many of which are set forth below, refer to a compound capable of modulating, either directly or indirectly, the CRF_1 receptor in an *in vitro* assay, an *in vivo* model, and/or other means indicative of therapeutic efficacy. The terms also refer to a compound that exhibits at least some therapeutic benefit in a human subject.

[0163] The phrase "in a sufficient amount to effect a change" means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject's feeling of well-being).

[0164] The "activity" of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term "proliferative activity" encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

[0165] "Substantially pure" indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, "substantially pure" refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

[0166] The terms "specifically binds" and "selectively binds," when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample. The antibody, or binding composition derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen, or a variant or mutein thereof, with an affinity that is at least two-fold greater, at least 10-times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antibody, or binding composition derived therefrom. In embodiments, the antibody will have an affinity that is greater than about 10^9 liters/mol, as determined by, e.g., Scatchard analysis (Munsen, et al. (1980) Analyt. Biochem. 107:220-239).

[0167] The terms "DNA," "nucleic acid," "nucleic acid molecule," "polynucleotide" and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, messenger RNA (mRNA),

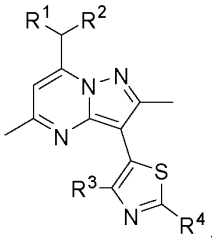
complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

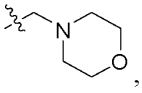
[0168] As used herein, the terms "variants" and "homologs" are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced (e.g., muteins); for example, the change is generated in the laboratory by human intervention ("hand of man"). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

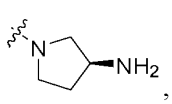
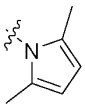
[0169] The term "muteins" as used herein refers broadly to mutated recombinant proteins. These proteins usually carry single or multiple amino acid substitutions and are frequently derived from cloned genes that have been subjected to site-directed or random mutagenesis, or from completely synthetic genes.

II. Compounds

[0170] In an aspect provided herein, is a compound of Formula (I):

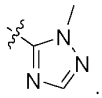


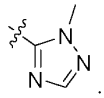
, or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,

 , , or  . R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–In embodiments, the inhibitor forms an irreversible bond with the amino acid residue. In embodiments, the bond is a covalent bond.

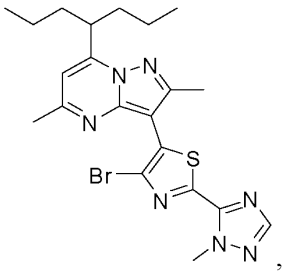
[0171] In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

[0172] In certain embodiments, R^3 is Cl, Br, or methyl.

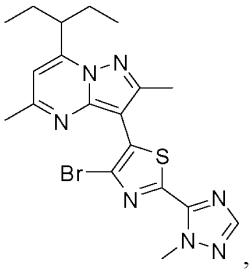
[0173] In certain embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  .

[0174] In certain embodiments, R^4 is morpholin-4-yl or  .

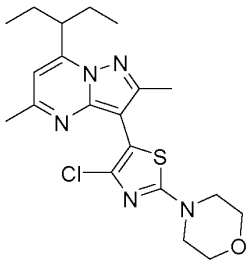
[0175] In certain embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

[0176] In certain embodiments, the compound is  , or a pharmaceutically acceptable salt thereof.

[0177] In certain embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0178] In certain embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0179] In one aspect described herein, there is a method of treating a subject in need thereof comprising administering an astressin or a pharmaceutically acceptable salt or solvate thereof. An astressin generally refers to a nonselective corticotropin releasing hormone antagonist that reduces the synthesis of ACTH and cortisol.

[0180] In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating congenital adrenal hyperplasia (CAH) in a subject in need thereof, the method comprising: (i) measuring a hormone level in the subject in need thereof; (ii) administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof; and repeating steps (i) and (ii) until the hormone level reaches a pre-determined range followed by a maintenance therapy of a daily dosing of said astressin.

[0181] In one aspect described herein, there is a method of improving hyperandrogenic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of treating menstrual irregularity, ovulatory dysfunction or infertility, in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a method of improving metabolic symptoms in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto; or a pharmaceutically acceptable salt or solvate thereof.

[0182] In one aspect described herein, there is a method of improving quality of life in a subject in need thereof, comprising administering an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

III. Pharmaceutical Compositions

[0183] In an aspect, there is provided a pharmaceutical composition, including a compound as described herein, including embodiments, or the structural Formula (I), and a pharmaceutically acceptable excipient.

[0184] The compounds (e.g., CRF_1 inhibitors/antagonists) of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are "pharmaceutical compositions" comprising a compound (e.g., CRF_1 inhibitor(s)/ antagonist(s)) and one or more pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients. In certain embodiments, the compound (e.g., CRF_1 inhibitor/antagonist) are present in a therapeutically acceptable amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

[0185] In one aspect described herein, there is a pharmaceutical composition in the form of a capsule comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof. In one aspect described herein, there is a pharmaceutical composition in the form of a tablet comprising an astressin or a variant having at least about 70% identity thereto, or a pharmaceutically acceptable salt or solvate thereof.

[0186] The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

[0187] The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of CRF_1 function) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

[0188] The tablets, capsules and the like suitable for oral administration may be uncoated or coated to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for

controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly(methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

[0189] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0190] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

[0191] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

[0192] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting

agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

[0193] The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

[0194] The pharmaceutical compositions typically comprise a therapeutically effective amount of a CRF_1 inhibitor/antagonist contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

[0195] After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container

(e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

[0196] Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a CRF_1 inhibitor/antagonist, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

[0197] Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., CRF_1 inhibitor/antagonist) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

[0198] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

[0199] The present disclosure contemplates the administration of the compound (e.g., CRF_1 inhibitor/antagonist) in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

[0200] The compound (e.g., CRF_1 inhibitor/antagonist) contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

IV. Methods

[0201] In certain embodiments, provided herein are methods for treating or preventing a disease comprising administering an effective amount of a compound of Formula (I), or an isotopic variant thereof or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0202] In one embodiment, provided herein are methods for treating or preventing a tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a benign tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing a malignant tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing an adrenal rest tumor, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0203] In one embodiment, provided herein are methods for treating or preventing infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for treating or preventing male infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm count, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm motility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are methods for improving or increasing sperm morphology, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, provided herein are

methods for treating or preventing female infertility, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0204] In one embodiment, provided herein are methods for treating or preventing a proliferative or hyperproliferative disease or disorder, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a cancer of the breast, skin, prostate, cervix, uterus, ovary, testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system.

[0205] In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenstrom's macroglobulinemia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, aligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mutinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and

inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prol actin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonserninoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcorna; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but

not limited to, renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (*See* Fishman *et al.*, 1985, *Medicine*, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy *et al.*, 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

[0206] Depending on the disorder, disease, or condition to be treated, and the subject's condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration as described elsewhere herein.

[0207] The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. Recommended routes of administration for the second active agents are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

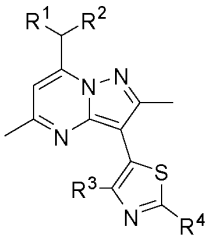
[0208] In one embodiment, provided herein are methods for treating or preventing testicular adrenal rest tumors (TART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

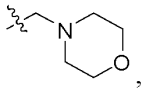
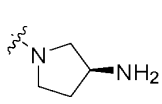
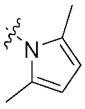
[0209] In one embodiment, provided herein are methods for treating or preventing ovarian adrenal rest tumors (OART) in a subject, comprising administering a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, wherein the subject has congenital adrenal hyperplasia (CAH).

[0210] In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

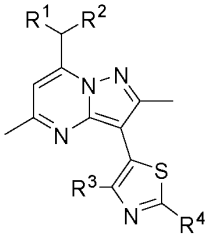
[0211] In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

[0212] In an aspect provided herein, is a method of treating or preventing testicular adrenal rest tumors (TART), comprising administering to a subject in need thereof a compound of structural Formula (I):



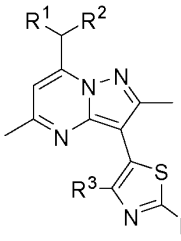
, or a pharmaceutically acceptable salt thereof. R^1 and R^2 are independently ethyl or n-propyl. R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy. R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  , , or  . R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0213] In an aspect provided herein, is a method of treating or preventing ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):



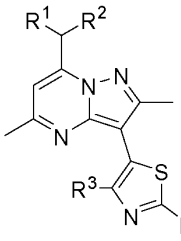
, or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments.

[0214] In an aspect provided herein, is a method of decreasing or reducing adrenocorticotropic hormone (ACTH) levels in a subject in need thereof, comprising administering to the subject contacting the ACTH with a compound of structural Formula (I):

 , or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 60% of the subjects demonstrate reduction in ACTH.In certain embodiments, at least about 70% of the subjects demonstrate reduction in ACTH. In certain embodiments, at least about 80% of the subjects demonstrate reduction in ACTH. In embodiments, at least about 10% of subjects were in the standard or normal range for ACTH after treatment.

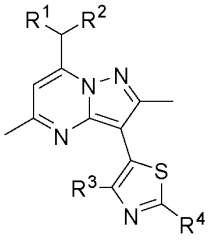
[0215] In embodiments, at least about 20% of subjects were in the standard or normal range for ACTH after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for ACTH after treatment. In certain embodiments, ACTH levels are decreased or reduced within about 30 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 1 hour post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 90 minutes post dosing. In certain embodiments, ACTH levels are decreased or reduced within about 2 hours post dosing.

[0216] In an aspect provided herein, is a method of decreasing or reducing 17α-hydroxyprogesterone (17-OHP) levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

 , or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 60% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 70% of the subjects demonstrate reduction in 17-OHP. In certain embodiments, at least about 80% of the subjects demonstrate reduction in 17-OHP. In embodiments, at least about 30% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 40% of subjects were in the standard

or normal range of 1200 ng/dL after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 60% of subjects were in the standard or normal range of 1200 ng/dL after treatment. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment. In embodiments, at least about 60% of subjects demonstrated an at least about 25% reduction in 17-OHP after treatment.

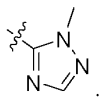
[0217] In an aspect provided herein, is a method of decreasing or reducing androstenedione levels in a subject in need thereof, comprising administering to the subject a compound of structural Formula (I):

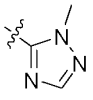


, or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. R^1, R^2, R^3 and R^4 are as described herein, including embodiments. In certain embodiments, at least about 50% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 60% of the subjects demonstrate reduction in androstenedione.In certain embodiments, at least about 70% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 80% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least about 90% of the subjects demonstrate reduction in androstenedione. In certain embodiments, at least 100% of the subjects demonstrate reduction in androstenedione. In embodiments, at least about 30% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 40% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 50% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least 60% of subjects demonstrated an at least about 25% reduction in androstenedione after treatment. In embodiments, at least about 30% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 40% of subjects were in the standard or normal range for androstenedione after treatment. In embodiments, at least about 50% of subjects were in the standard or normal range for androstenedione after treatment.

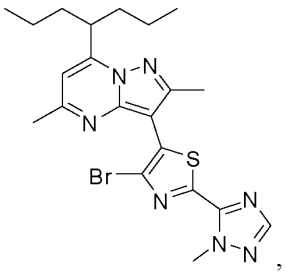
[0218] In certain embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl.

[0219] In certain embodiments, R^3 is Cl, Br, or methyl.

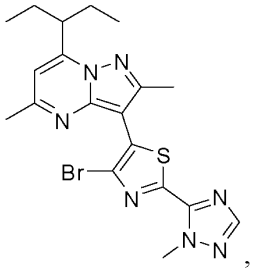
[0220] In certain embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  .

[0221] In certain embodiments, R^4 is morpholin-4-yl or  .

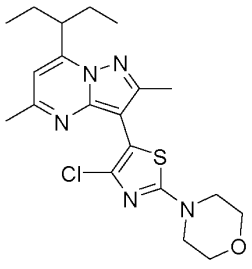
[0222] In certain embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl.

[0223] In certain embodiments, the compound is  , or a pharmaceutically acceptable salt thereof.

[0224] In certain embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0225] In certain embodiments, the compound is

 , or a pharmaceutically acceptable salt thereof.

[0226] In certain embodiments, a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is cyclically administered to a patient. Cycling therapy involves the administration of an active agent or a combination of active agents for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or

more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

[0227] In certain embodiments, in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein (e.g., treatment or prevention of testicular adrenal rest tumors (TART) or treatment or prevention of ovarian adrenal rest tumors (OART)), an appropriate dosage level of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof generally is ranging from about 1 mg to 3000 mg, from about 1 mg to 2000 mg, from about 1 mg to 1000 mg, from about 1 mg to about 500 mg, from about 5 mg to about 500 mg, from about 5 mg to about 400 mg, from about 5 mg to about 300 mg, from about 5 mg to about 250 mg, from about 5 mg to about 200 mg, from about 50 mg to about 200 mg, from about 10 mg to about 400 mg, from about 5 mg to about 25 mg, from about 10 mg to about 25 mg, or from about 25 to about 200 mg, which can be administered in single or multiple doses. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about

155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 800 mg, or about 1000 mg/day.

[0228] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is

administered in an amount of about 230 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or

prodrug thereof is administered in an amount of about 390 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg.

[0229] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, or about 1000 mg.

[0230] For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing from about 1.0 mg to about 1,000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60

mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof for the symptomatic adjustment of the dosage to the patient to be treated. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 50 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, for oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets or capsules containing about 200 mg of a compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate,

hydrate, or prodrug thereof.The pharmaceutical compositions can be administered on a regimen of one (1) to four (4) times per day, including once, twice, three times, and four times per day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 990 mg, about 990 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered once per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg,

about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg,

about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 755 mg, about 760 mg, about 765 mg, about 770 mg, about 775 mg, about 780 mg, about 785 mg, about 790 mg, about 795 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered three times per day.

[0231] In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of one day. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of two days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of three days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of four days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of five days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of six days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of seven days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of eight days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of nine days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of ten days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 11 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 12 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 13 days. In some embodiments, the compound of Formula (I), or an isotopic variant

thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 14 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 15 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 16 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 17 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 18 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 19 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 20 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 21 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 22 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 23 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 24 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 25 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 26 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 27 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 28 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 29 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered for a period of 30 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 31 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 32 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 33 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 34 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 35 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 36 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 37 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 38 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 39 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 40 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 41 days. In some embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered over a period of 42 days or more.

[0232] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate,

hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days.

[0233] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an

amount of about 270 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I),

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 14 days.

[0234] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is

administered in an amount of about 25 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 140 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the

compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is

administered in an amount of about 450 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 14 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 14 days.

[0235] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 28 days. In certain

embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug

thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 28 days. In certain

embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 28 days.

[0236] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt,

solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 280 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 28

days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt,

solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 28 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 28 days.

[0237] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 255 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg once daily for a period of up to at least

about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg once daily for a period of up to at least

about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg once daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg once daily for a period of up to at least about 42 days.

[0238] In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 5 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 10 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 15 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 20 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 25 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 50 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 100 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 150 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 200 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 210 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 220 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 230 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 240 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 250 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 260 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 270 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 420 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 290 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 300 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 310 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 320 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 330 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 340 mg twice daily

for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 350 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 360 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 370 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 380 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 390 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 400 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 450 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 500 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 600 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 700 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 800 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 900 mg twice daily for a period of up to at least about 42 days. In certain embodiments, the compound of Formula (I), or an isotopic variant thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered in an amount of about 1000 mg twice daily for a period of up to at least about 42 days.

[0239] In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, or about 400 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered twice per day. In some embodiments, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, or about 800 mg of the compound of Formula (I), or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered at least once per day.

[0240] In certain embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0241] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally.

[0242] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet.

[0243] In certain embodiments, from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0244] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a

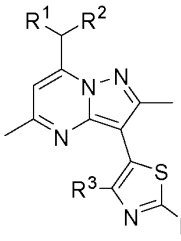
dose of from about 10 mg/day to about 400 mg/day is administered to the subject.In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0245] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day.

[0246] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 6 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 5 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 3 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 1 hour before sleep. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep.

[0247] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

[0248] In another aspect is provided a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I): and a pharmaceutically acceptable excipientcomprising with a compound as described herein, including embodiments, or the structural Formulae (I) and a pharmaceutically acceptable excipient:



, or a pharmaceutically acceptable salt thereof. R^1, R^2, R^3, and R^4 are as described herein, including embodiments.

[0249] In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0250] In certain embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0251] In certain embodiments, the pharmaceutical composition is administered orally.

[0252] In certain embodiments, the pharmaceutical composition is formulated as a capsule or tablet. In certain embodiments, the capsule or tablet comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360

mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 50 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the capsule or tablet comprises about 200 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0253] In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0254] In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 25 mg/day to about 1000 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day is administered to the subject. In certain embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

[0255] In certain embodiments, the pharmaceutical composition is administered in the fed state. In certain embodiments, the pharmaceutical composition is administered in the fasted state. In certain embodiments, the pharmaceutical composition is administered at least once per day.

[0256] In certain embodiments, the pharmaceutical composition is administered at bedtime. In certain embodiments, the pharmaceutical composition is administered less than about 6 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 5 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 3 hours before sleep. In certain embodiments, the

pharmaceutical composition is administered less than about 2 hours before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 1 hour before sleep. In certain embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep.

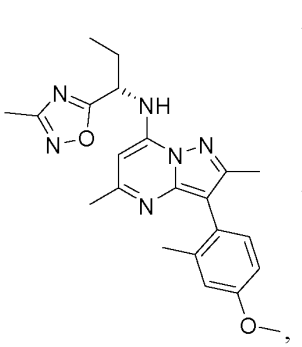
[0257] In certain embodiments, the pharmaceutical composition is administered in the evening. In certain embodiments, the pharmaceutical composition is administered at about 10 pm at night.

[0258] In certain embodiments, the subject has congenital adrenal hyperplasia (CAH).

[0259] In certain embodiments, the size and/or number of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced. In certain embodiments, the size of the tumors is decreased or reduced.

[0260] In certain embodiments of the methods disclosed herein, the method further comprises administering to the subject an additional chemotherapeutic agent.

[0261] In certain embodiments, the the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In certain embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In certain embodiments, the mineralocorticoid is fludrocortisone. In certain embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In certain embodiments, the CRF_1 antagonist is: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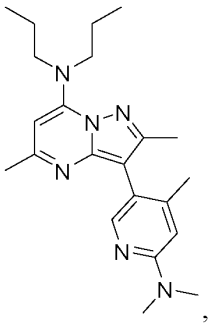
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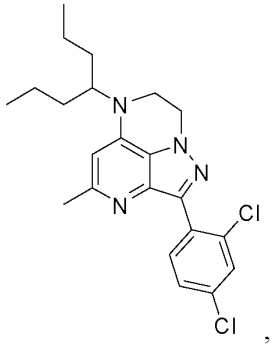
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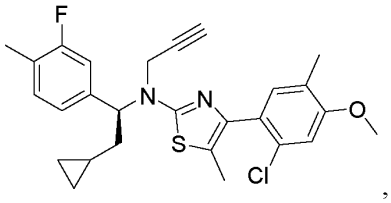
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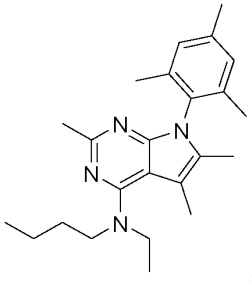
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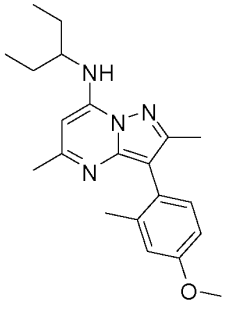
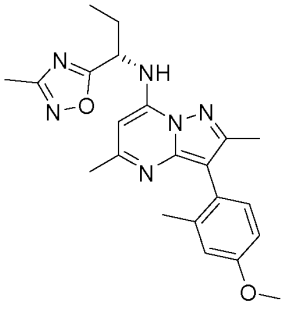

, or a

pharmaceutically acceptable salt thereof. In certain embodiments, the CRF_1 antagonist is



, or a pharmaceutically acceptable salt thereof.

[0262] In certain embodiments of the methods disclosed herein, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof. In certain embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0263] In certain embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In certain embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In certain embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0264] In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. In some embodiments, a tablet comprises a solid carrier or an adjuvant. Liquid

pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil, or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. In some embodiments, a capsule comprises a solid carrier such as gelatin.

[0265] In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer's injection, or Lactated Ringer's injection. In some embodiments, preservatives, stabilisers, buffers, antioxidants, and/or other additives are included as required.

[0266] In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

[0267] The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, 2nd Edition, Rathbone *et al.*, Eds., Marcel Dekker, Inc.: New York, NY, 2008).

[0268] The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

[0269] The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

[0270] In certain embodiments, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

A. Oral Administration

[0271] The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

[0272] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline

cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[0273] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[0274] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[0275] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[0276] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not

limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[0277] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[0278] The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film

coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[0279] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[0280] The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[0281] Coloring and flavoring agents can be used in all of the above dosage forms.

[0282] The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

[0283] The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[0284] The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be

prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

[0285] The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[0286] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methy1-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[0287] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl-and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[0288] When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungi static concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[0289] In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[0290] The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[0291] The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[0292] Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and metliacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[0293] Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

V. Examples

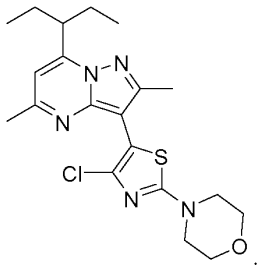
[0294] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Example 1. A Phase 2, Open-Label Study to Evaluate the Efficacy and Safety of Compound 1 in Subjects with Testicular Adrenal Rest Tumors

[0295] Testicular adrenal rest tumors (TART) is a common complication in congenital adrenal hyperplasia (CAH) that is caused by adrenocorticotropin hormone (ACTH)–driven overstimulation of aberrant adrenal cells within the testes and results in impaired spermatogenesis and infertility. TARTS can be found anywhere on the testes, though a typical (very common) location is within the mediastinum. This is a particularly problematic location. Because of the central location of TARTs being in the mediastinum, compression of the nearby seminiferous tubules is common and can lead to obstructive azoospermia, irreversible damage to surrounding tissue, and permanent infertility in males.

[0296] Current treatment for TART consists of chronic high-dose glucocorticoids, a problematic therapy with significant side effects and a narrow therapeutic window. Given the serious nature of TART and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with TART. Compound 1, a high-affinity and selective small-molecule antagonist of the corticotropin-releasing factor type-1 (CRF_1) receptor, may be effective in blocking ACTH synthesis, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-hydroxyprogesterone (17-OHP) in subjects with CAH (FIG. 12A-12B). Compound 1 has been shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. These promising results provide a rationale for investigating the use of Compound 1 in the treatment of TART, in combination with replacement glucocorticoids and mineralocorticoids.

[0297] The structure of Compound 1 is:



[0298] Building upon the 2 completed Phase 1 studies of Compound 1 in healthy volunteers and the ongoing Phase 2 proof-of-concept study of Compound 1 in subjects with CAH, this Phase 2 will study Compound 1 specifically in male CAH subjects with TART for the first time. A sample size of approximately 12 subjects was selected to provide sufficient data for an initial evaluation of efficacy and safety in subjects with TART while maintaining feasible subject recruitment goals for this rare condition. Given the rarity of the disease and thus the small sample size that can be recruited, this study will be open label, and all enrolled subjects will receive active study drug. Subjects will serve as their own controls in that their outcome measures after 12 weeks of study drug dosing will be compared to their baseline measures.

[0299] The schedule of study visits (every 2 weeks through Week 4, then every 4 weeks for the remainder of the study) provides an appropriate balance between minimizing subject burden and closely monitoring subject safety and response to therapy. The 4-week post-treatment washout period will allow for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

[0300] The specification of study drug dosing at 10pm and after consumption of a snack is based on information from the Phase 1 studies in healthy volunteers. The plasma C_{max} (maximum concentration) for Compound 1 in the Phase 1 studies occurred approximately 5 hours after dosing. Therefore, Compound 1 will be dosed daily at 10pm in this study in order to achieve peak plasma study drug concentration at the time of day when most adrenal androgens are produced. Subjects will consume a standardized snack before taking study drug because the Phase 1 studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety. (**FIGS. 1A-1B**).

Objectives	Endpoints
Primary	
• To assess the efficacy of Compound 1 in subjects with TART	• Reduction in the size/volume of TART on testicular ultrasound from screening to Week 12
Secondary	
• To evaluate the safety of Compound 1 in subjects with TART	• Adverse events (AEs), serious adverse events (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs) • Physical examination findings • Vital signs • Changes in electrocardiogram (ECG) • Changes in clinical laboratory values
• To assess the pharmacodynamic (PD) biomarker effects of Compound 1	• Changes in plasma concentrations of key PD biomarkers, including ACTH, 17-OHP, testosterone, androstenedione, luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, sex hormone–binding globulin (SHBG), renin, and aldosterone from baseline to Week 12
• To assess changes on semen analysis	• Changes in sperm count, morphology, and motility from baseline to Week 12
• To assess changes in metabolism	• Changes in metabolic parameters, including fasting glucose, HbA1c, insulin sensitivity, and lipid profile (including LDL cholesterol, HDL cholesterol, and triglycerides), from baseline to Week 12 • Changes in body weight, body mass index (BMI), waist circumference, and blood pressure
• To evaluate changes in quality of life (QoL) and mood	• Changes in QoL measured using the Short Form 36 (SF-36) • Changes in mood measured using the Hospital Anxiety and Depression Scale (HADS)

Study Population

[0301] Approximately 12 male subjects with TART will be enrolled at approximately 6 investigative sites in the United States, United Kingdom, and possibly other countries. Up to 12 additional subjects may be added to further evaluate specific safety, PD, or efficacy findings.

Eligibility Criteria

Inclusion Criteria

- Adult male subjects aged 18 to 30, inclusive
- Documented historical diagnosis of CAH based on documented genetic mutation or historical documentation of elevated 17-OHP
- Diagnosis of TART via testicular ultrasound and/or magnetic resonance imaging (MRI) at screening with ≥1 lesion(s) measuring ≥2 cm in diameter
- On a stable regimen of GC replacement for ≥30 days before baseline
- Agree to follow contraception guidelines and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug
- Subject is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Exclusion Criteria

- Any clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
  - A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
  - Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2
  - Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
  - Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
- Any clinically significant psychiatric disorders, including any current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months
- HADS score >12 for either depression or anxiety
- At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at screening and baseline (eg,

C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)

- Clinically significant and abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:
  - Clinically meaningful abnormal ECG results, in the opinion of the Investigator
  - Fridericia-corrected QT interval (QTcF) >450 msec
  - Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
  - Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- A history that includes bilateral adrenalectomy or hypopituitarism
- Use of any other investigational drug within 30 days or 5 half-lives, whichever is longer, before initial screening
- Require use of prohibited concomitant medications, including strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids, hydrocortisone, and dexamethasone) within 30 days or 5 half-lives (whichever is longer) of first dose of study drug. Medications that are sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before the first dose of study drug.
- Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

Study Duration

[0302] The expected duration of study participation for each subject is up to approximately 20 weeks. This includes a screening period of ≤4 weeks, a treatment period of 12 weeks, and a safety follow-up period of 4 weeks.

Study Design

[0303] This is a Phase 2, open-label efficacy and safety study of Compound 1 for the treatment of TART. All subjects will receive a daily oral dose of Compound 1 for 12 weeks.In-clinic study visits will occur for screening and at Day 1 (baseline) and Weeks 2, 4, 8, 12 (end of treatment), and 16 (follow-up).

Dose, Route, Regimen

[0304] All subjects will receive a daily oral dose of Compound 1 for 12 weeks. Subjects will receive 600 mg/day during the first 2 weeks and 1000 mg/day during the remaining 10 weeks of the treatment period. Study drug will be taken daily at 10pm (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack.

[0305] On mornings of study visits with 8am blood draws for laboratory assessments, subjects should take their morning glucocorticoid replacement after the blood draws. For all other days during the study, subjects may take their morning glucocorticoid replacement at their usual time (generally between 6am and 8am).

[0306] If a subject experiences a Grade 3 or higher TEAE considered at least possibly related to study drug, the Investigator may reduce the subject's daily dose of Compound 1 down in increments of 200 mg. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria.

Investigational Drug

[0307] Compound 1 is a small-molecule CRF_1 receptor antagonist and will be supplied as 200-mg, size 1, white, hard gelatin capsules.

Example 2.

[0308] Since elevated ACTH is the primary driver for TART growth, blocking ACTH synthesis using Compound 1, a small-molecule antagonist of the CRF_1 receptor, may be effective in reducing ACTH levels, thereby reducing the size of testicular lesions in TART and reducing the need for chronic supraphysiologic doses of GCs. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. 12A-12B). The safety profile of Compound 1 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH is currently ongoing.

Nonclinical Toxicology of Compound 1

[0309] The nonclinical safety profile of Compound 1 has been evaluated in repeat-dose range-finding and definitive toxicology studies of up to 91 days in duration in rats and dogs using the clinically relevant route (oral) and schedule of administration (once daily). In rats and beagle dogs administered oral Compound 1 once daily for 91 consecutive days at doses up to 2000 mg/kg/day, toxicologic findings were all mild and limited to the male reproductive tract, and all Compound 1-related findings were reversible following a 6-week treatment-free recovery period.

[0310] Additionally, a fertility toxicology study was conducted in rats. In this study, male rats were administered oral Compound 1 once daily at 0, 5, 20, or 1000 mg/kg for 85 to 87 days (70 days before mating, during mating, and ≤4 days between mating and necropsy). Male reproductive performance (mean day of mating, mating and fertility indices, and conception rates) was unaffected by Compound 1 treatment. Untreated females mated with the Compound 1-treated males had no ovarian and uterine effects.

[0311] In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay have also been conducted.

Clinical Experience with Compound 1

[0312] To date, a total of 53 subjects, all healthy adults aged 21 to 65 years, have been treated with at least 1 dose of Compound 1 in 2 Phase 1 studies. The first-in-human study of Compound 1 (Study I3C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study I3C-FW-BLAB) evaluated repeat doses of 50 mg, 100 mg, or 200 mg Compound 1 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs). Compound 1 has been well tolerated in healthy human subjects, with no SAEs, AEs leading to discontinuation, or dose-limiting toxicities (DLTs). A maximum tolerated dose has not been reached in humans.

[0313] An ongoing Phase 2 open-label study (Study Compound 2) is currently evaluating the safety and efficacy of Compound 1 dosed once daily for 6 weeks in adults with classic CAH. In the initial Cohort A of this study, all subjects are dosed starting at 200 mg/day for 14 days, escalating for each subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLTs at the previous dose level. (**FIGS. 2-3**).

Known Potential Risks

[0314] Because the reversible testicular effects (degeneration/atrophy) observed in rats and dogs treated with high-dose Compound 1 (2,000 mg/kg/day) are likely associated with on-target (mechanism-driven) effects, these effects are likely to be relevant to human risk. However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical laboratory markers of testicular function (LH and FSH) when Compound 1 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Clinical laboratory measures

of testicular function (LH, FSH, inhibin B, and SHBG) will be assessed throughout this study to monitor the risk of testicular injury. Testicular ultrasounds and semen analysis will also be performed at screening/baseline and the end of the treatment period.

[0315] Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the Phase 1 clinical studies. Clinical laboratory measures of liver chemistry will be assessed throughout this study, and strict individual treatment stopping criteria for liver chemistry findings are in place.

[0316] Compound 1-induced effects on the thyroid gland were noted in dogs after 91 days of high-dose (2,000 mg/kg/day) treatment but not in any other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) were not evaluated in the Phase 1 studies but will be monitored throughout this study.

Known Potential Benefits

[0317] Early clinical studies suggests that Compound 1 is effective as a CRF_1 receptor antagonist, a mechanism of action that supports the clinical investigation of Compound 1 for treatment of TART. In CAH, this mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced dose-dependent reductions in ACTH and 17-OHP in subjects with CAH (FIG. 12A-12B).

Assessment of Potential Risks and Benefits

[0318] The mild and reversible toxicologic effects of Compound 1 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a CRF_1 receptor antagonist, Compound 1 is intended to reduce abnormally elevated ACTH levels, which in TART drives overstimulation of aberrant adrenal cells within the testes. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. In TART, where baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

[0319] Given the serious nature of TART and the limitations (and risks) of chronic steroid therapy, new treatment modalities are needed for patients with TART. Given the acceptable safety and tolerability profile of Compound 1 in healthy volunteers from the Phase 1 program, the low probability of demonstrating meaningful PD marker changes in healthy subjects, and the lack of any clear benefit to exposing more healthy subjects to study drug, the Sponsor believes the benefit-to-risk profile favors the entry of Compound 1 into Phase 2 in subjects with TART.

Example 3. Congenital Andrenal Hyperplasia (CAH)

[0320] CAH results from a genetic defect in the 21-hydroxylase enzyme. CAH patients are thus unable to produce cortisol. Without cortisol to provide negative feedback, patients over-produce ACTH. High ACTH promotes the overproduction of potent androgens (male sex hormones). Without wishing to be bound by theory, Compound 1 blocks CRF_1 receptor to prevent ACTH release by the pituitary and associated drive on the hypothalamic-pituitary-adrenal axis. Replacement of cortisol to physiological levels will correct cortisol deficiency, however, will not lower ACTH, resulting in hyperplasia of adrenal gland and associated overproduction of adrenal androgens.

[0321] As shown in **FIGS. 4** and **5A-5B**, the attenuation of ACTH demonstrates target engagement and functional CRF_1 receptor antagonism. 80% of subjects demonstrated reduction in ACTH. 70% of subjects demonstrated > 25% reduction in ACTH. 30% of subjects were in the normal range (*) after treatment with a CRF_1 receptor antagonist.

[0322] FIGS. 6 and **7A-7B** demonstrate "control" of disease based on standard guidelines, which would then allow steroid taper. 80% of subjects demonstrated reduction in 17-OHP. 50% of subjects demonstrated > 25% reduction in ACTH. 50% of subjects were in the guideline range (*; 1200 ng/dL) after treatment with a CRF_1 receptor antagonist.

[0323] FIGS. 8 and **9A-9B** demonstrate attenuation of morning rise in A4 upon treatment with a CRF1 antagonist, indicative of its ability to control excess androgen production and associated symptoms. 100% of subjects demonstrated reduction in androstenedione (at various doses). 60% of subjects demonstrated > 25% reduction in androstenedione. 50% of subjects were within the normal reference range after treatment with a CRF_1 receptor antagonist.

[0324] FIGS. 10A-10B show approximately 25% shrinkage in TART in a 25 year old male with classic congenital adrenal hyperplasia following 6 weeks treatment with a CRF_1 receptor antagonist.

[0325] FIGS. 11A-11B demonstrate Compound 1 is a potent, selective, and functional CRF_1 receptor antagonist. In in vitro and ex vivo studies, Compound 1 was determined to be a potent and selective CRF_1 receptor antagonist with high affinity and selective for the $hCRF_1$ receptor. Compound 1 was found to have functional potency to inhibit adenylate cyclase activity (CRF_1 receptor-mediated downstream cascade), demonstrating in vitro efficacy as a CRF_1 receptor antagonist. Compound 1 was found to significantly inhibit CRF-induced locomotor behavior in response to i.c.v. administration of CRF (**FIG. 11B**).

[0326] FIGS. 12A-12B demonstrate single pill of CRF_1 receptor antagonist (i.e., as described in US 2017/0020877 A1) improves ACTH and 17-OHP in CAH patients.

[0327] FIG. 13 shows the subject level hormone changes (ACTH, 17-OHP, and androstenedione) by dose of a CRF_1 receptor antagonist.

Example 4. Assess reduction in excess ACTH and adrenal steroid production

[0328] The objectives of the study are: to assess the ability of Compound 1 to reduce excess ACTH and adrenal steroid production in participants with classic CAH on a stable gluococorticoid regimen; to evaluate the safety and tolerability of tildacerfont in participants with classic CAH; and to evaluate the pharmacokinetics (PK) of tildacerfont.

ELIGIBILITY CRITERIA

[0329] Inclusion Criteria:

- Adult males and females 18 years or older
- Diagnosis of classic CAH due to 21-hydroxylase deficiency
- Morning 17OHP ≥800 ng/dL, before taking any morning GC dose
- On a stable regimen of gluococorticoid replacement for ≥30 days before enrollment

[0330] Exclusion Criteria:

- Clinically significant unstable medical condition, illness, or chronic disease within 30 days of screening
- Clinically significant psychiatric disorder
- History of bilateral adrenalectomy or hypopituitarism

STUDY DESIGN

[0331] FIG. 14 depicts the proof of concept and escalating QD dosing at 10 PM for Cohort A and the single dose level and BID dosing at 10 AM and 10 pm for Cohort B.

BASELINE CHARACTERISTICS

[0332] Table 1 provides a description of the baseline characteristics displayed by Cohort A and Cohort B. In Cohort A, 10 partcipants were enrolled and received at least 1 dose of Compound 1. One participant withdrew early because of an occupation-related scheduling conflict. In Cohort B, 9 participants were enrolled and received at least one dose of Compound 1. One participant was withdrawn upon discovery of a major protocol violation at Baseline and did not have postbaseline efficacy/PK data. Thus, baseline characteristics are calculated for n=8 in Cohort B. One participant in Cohort B was taking both HC and prednisone.

Table 1 – Baseline characteristics of each cohort

Parameter	Cohort A (n=10)	Cohort B (n=8)
Demographics		
Age (years), mean (range)	39.3 (24-66)	36.8 (19-66)
Sex	5M, 5F	1M, 7F
Bmi (kg/m^2), mean ± SD	31.5 ± 12.0	31.1 ± 6.7

Daily GC dose (mg HC equivalents), mean range Types of GCs	28 (13-40) 4 JC, 3 pred, 3 dex	35 (20-50) 2HC, 4 pred, 3 dex
17OHP at screening[a] (ng/dl), mean ± SD	5,985 ± 6,347	4,592 ±4,624

Abbreviations: 17OHP: 17-hydroxyprogesterone; BMI: body mass index; dex: dexamethasone; F: female; GC: glucocorticoid; HC: hydrocortisone; M: male; pred: prednisone; SD: standard deviation.
a 17OHP reference ranges: 27-199 ng/dL males, 15-290 ng/dL females.

SAFETY

[0333] Across both cohorts, Compound 1 was generally well tolerated. The most common type of adverse event (AE) was gastrointestinal disorders There were no serious AEs and no AEs leading to withdrawal.

PHARMACOKINETICS

[0334] Over a wide range of doses (200 to 1000 mg QD), Compound 1exhibited a predictable, dose-dependent PK profile.

EFFICACY

[0335] FIG. 15A-15D show the changes in levels of Androstenedione (A4) across both cohorts. Levels of A4 improved at ≥1 dose level for 10 out of 10 participants in Cohort A and 6 out of 8 participants in Cohort B. Excess A4 is associated with clinical sequelae in CAH. Attenuation of A4 demonstrates control of adrenal androgen.

[0336] FIG. 16A-16D show the changes in levels of 17-hydroxyprogesterone (17-OHP) across both cohorts. Levels of 17OHP improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 6 out of 7 participants in Cohort B. 17OHP is a critical hormone in CAH diagnosis and management. Attenuation of 17OHP demonstrates control of adrenal steroid production.

[0337] FIG. 17A-17D show the changes in levels of adrenocorticotropic hormone (ACTH) across both cohorts. Levels of ACTH improved at ≥1 dose level for 8 out of 10 participants in Cohort A and 5 out of 7 participants in Cohort B. Attenuation of ACTH demonstrates target engagement and fucntional CRF_1 receptor antagonism.

Table 2 – Percentage change from baseline in ACTH, 17OHP and A4.

	Cohort A			Cohort B
	200 mg QD (Week 2)	600 mg QD (Week 4)	1000 mg QD (Week 6)	200 mg BID (Week 2)
ACTH	-25.7 (±51.6)	-60.1 (±37.5)	-32.7 (±47.0)	-36.5 (±58.0)
17OHP	+22.2 (±172.3)	-23.7 (±64.2)	-13.8 (±74.7)	-47.8 (±63.3)
A4	-12.1 (±47.4)	-33.2 (±36.5)	-28.6 (±44.6)	-16.0 (±81.4)

CONCLUSIONS

[0338] Compound 1, a potent and selective CRF_1 receptor antagonist, offers a novel nonsteroidal oral treatment approach for CAH. Compound 1 was well tolerated and efficacious in reducing excess ACTH, 17OHP, and androstenedione in patients with classic CAH.

Compound 1 exhibited a predictable, dose-dependent PK profile suitable for the target population.

[0339] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

CROSS-REFERENCE

[0001] This application is a continuation of U.S. Application No. 18/941,832, filed November 8, 2024, which is a continuation of U.S. Application No. 17/667,285, filed on February 8, 2022, which is a continuation of U.S. Application No. 17/081,694 filed on October 27, 2020, which issued as U.S. Pat. No. 11,304,950 on April 19, 2022, and which is a continuation of International Application No. PCT/US2019/029486 filed on April 26, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/663,951, filed April 27, 2018, and U.S. Provisional Patent Application No. 62/822,815, filed March 23, 2019, each of which is entirely incorporated herein by reference.

BACKGROUND

[0002] Corticotropes are basophilic cells in the anterior pituitary that produce melanocyte-stimulating hormone, adrenocorticotropic hormone (ACTH) and lipotropin. The cells produce pro-opiomelanocortin (POMC) which undergoes cleavage to ACTH and β-lipotropin (β-LPH). These cells respond to corticotropin-releasing factor (CRF) and make up about 20% of the cells in the anterior pituitary. CRF is a releasing hormone that belongs to the corticotropin-releasing factor family and is the primary physiological regulator of proopiomelanocortin (POMC).

[0003] CRF is produced by parvocellular neuroendocrine cells within the paraventricular nucleus of the hypothalamus and is released at the median eminence from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamo-hypophyseal portal system. The portal system carries the CRF to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete ACTH and other biologically-active substances. ACTH, in turn, stimulates the synthesis of cortisol, glucocorticoids, mineralocorticoids and DHEA.

[0004] Testicular adrenal rest tumors (TART) and ovarian adrenal rest tumors (OART) are ACTH-responsive lesions of the testes and ovaries derived from adrenal tissue interchelated within these organs during embryogenesis. In response to high ACTH, hyperplasia of this tissue occurs, resulting in single or multiple lesions that may cause pain and infertility. The identification of compounds that modulate CRF function and downstream processes is an ongoing challenge. Currently, there are no non-steroidal, non-surgical solutions to control, shrink, or reduce TART. Disclosed herein, *inter alia*, are solutions to these and other problems in the art.

SUMMARY

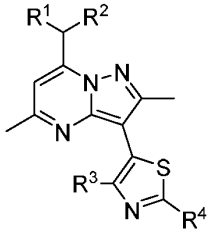
[0005] Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a serious genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), and adrenal androgens such as androstenedione (A4). CAH is an orphan condition with no FDA-approved therapy. To suppress androgen production, patients are often prescribed long-term supraphysiologic doses of glucocorticoid (GC), which has adverse effects and fail to suppress 17OHP and A4 in the majority of patients.

[0006] Compound 1 may be a potent, selective, nonsteroidal, oral corticotropin-releasing factor type-1 (CRF1) receptor antagonist that reduces excess ACTH, 17OHP, and A4 to improve clinical and biochemical sequelae of CAH. This may obviate the need for high dose steroids.

[0007] One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a corticotropin-releasing factor type-1 (CRF_1) antagonist or a pharmaceutically acceptable salt thereof.

[0008] In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

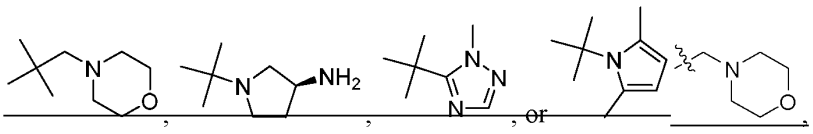
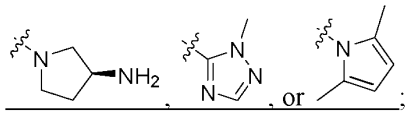
[0009] One aspect provided herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a compound of structural Formula (I):


(I), or a pharmaceutically acceptable salt thereof,

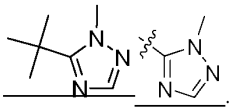
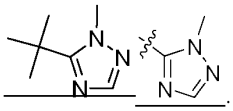
wherein:

R^1 and R^2 are independently ethyl or n-propyl;

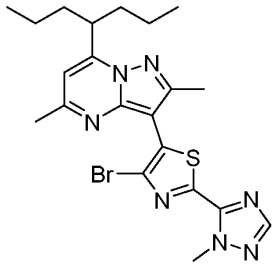
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  , or  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

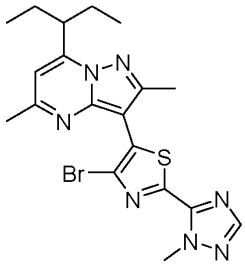
[0010] In some embodiments, R^3 is Cl, Br, methyl, or trifluoromethyl. In some embodiments, R^3 is Cl, Br, or methyl. In some embodiments, R^4 is Br, R^aR^bN–, pyridin-4-yl, morpholin-4-yl, or  . In some embodiments, R^4 is morpholin-4-yl or  .

[0011] In some embodiments, R^4 is hydrogen, Br, R^aR^bN– and R^a and R^b are independently C_1-C_3alkyl. In some embodiments, the compound is



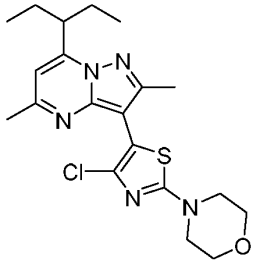
, or a pharmaceutically acceptable salt thereof.

[0012] In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0013] In some embodiments, the compound is



, or a pharmaceutically acceptable salt thereof.

[0014] In some embodiments, the subject has congenital adrenal hyperplasia (CAH). In some embodiments, the size and/or number of the tumors is decreased or reduced.

[0015] In some embodiments, from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 5 mg to about 25 mg of a compound of Formula (I), or a

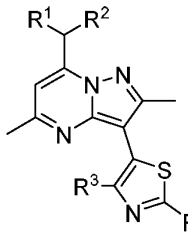
pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject. In some embodiments, from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject.

[0016] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 5 mg/day to about 1000 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 5 mg/day to about 25 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose from about 10 mg/day to about 400 mg/day is administered to the subject. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a dose of from about 100 mg/day to about 600 mg/day is administered to the subject.

[0017] In some embodiments, the compound is administered orally. In some embodiments, the compound is formulated as a capsule or tablet. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fed state. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the fasted state.

[0018] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at least once per day. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at bedtime. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 4 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 2 hours before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered less than about 30 minutes before sleep. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in the evening. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at about 10 pm at night.

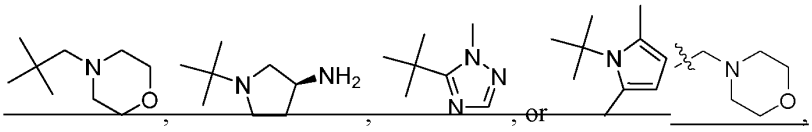
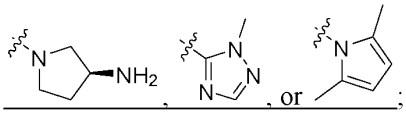
[0019] One aspect described herein is a method of treating or preventing testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART), comprising administering to a subject in need thereof a pharmaceutical composition, comprising a compound of structural Formula (I) and a pharmaceutically acceptable excipient:

 (I), or a pharmaceutically acceptable salt thereof,

wherein:

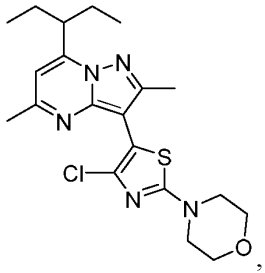
R^1 and R^2 are independently ethyl or n-propyl;

R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl, or methoxy; and

R^4 is hydrogen, Br, R^aR^bN–, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,  ,  ;

R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$–, $(CH_3)_3COC(O)NHCH_2CH_2$–, or $CH_3CH_2CH_2NHCH_2CH_2$–.

[0020] In some embodiments, the compound of Formula (I) has the structure:

 , or a pharmaceutically acceptable salt thereof.

[0021] In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 1000 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 5 mg to about 25 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 400 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises from about 100 mg to about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0022] In some embodiments, the pharmaceutical composition comprises about 5 mg, about 10 mg, about 15 mg, about 20 mg, 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg about 500 mg, or about 600 mg of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

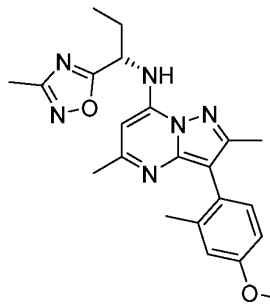
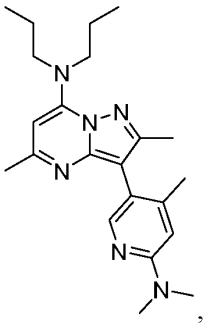
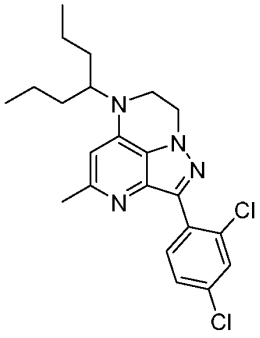
[0023] In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 1000 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 5 mg/day to about 25 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 10 mg/day to about 400 mg/day. In some embodiments, the pharmaceutical composition is administered at a dose of from about 100 mg/day to about 600 mg/day.

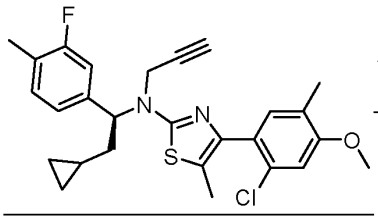
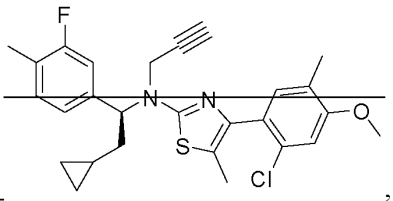
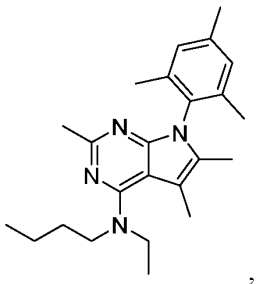
[0024] In some embodiments, the pharmaceutical composition is administered orally. In some embodiments, the pharmaceutical composition is formulated as capsule or a tablet. In some embodiments, the pharmaceutical composition is administered in the fed state. In some embodiments, the pharmaceutical composition is administered in the fasted state. In some embodiments, the pharmaceutical composition is administered at least once per day.

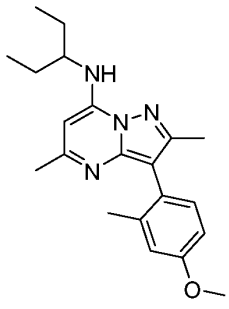
[0025] In some embodiments, the pharmaceutical composition is administered at bedtime. In some embodiments, the pharmaceutical composition is administered less than about 4 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 2 hours before sleep. In some embodiments, the pharmaceutical composition is administered less than about 30 minutes before sleep. In some embodiments, the pharmaceutical composition is administered in the evening. In some embodiments, the pharmaceutical composition is administered at about 10 pm at night.

[0026] In some embodiments, the method further comprises administering to the subject an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a glucocorticoid, a mineralocorticoid, an ACAT1 inhibitor, or an anti-androgen. In some embodiments, the glucocorticoid is beclomethasone, betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. In some embodiments, the mineralocorticoid is fludrocortisone.

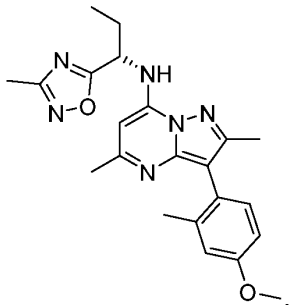
[0027] In some embodiments, the additional chemotherapeutic agent is another CRF_1 antagonist. In some embodiments, the CRF_1 antagonist is

 ,  ,  , SSR-126374,

 ,  ,  , or

 , or a pharmaceutically acceptable salt thereof.

[0028] In some embodiments, the CRF_1 antagonist is

 , or a pharmaceutically acceptable salt thereof.

[0029] In some embodiments, the method further comprises an additional treatment selected from surgical resection of the tumors and radiation therapy, or a combination thereof.

[0030] In some embodiments, the additional therapy is surgical resection and the surgical resection is prior to, after, and/or concurrent with administration of the compound of structural

Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof.

[0031] In some embodiments, the surgical resection is prior to administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the surgical resection is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0032] In some embodiments, the additional treatment is radiation therapy and the radiation therapy is prior to, after, and/or concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition, or any combination thereof. In some embodiments, the radiation therapy is prior to administration of the CRF_1 antagonist of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0033] In some embodiments, the radiation therapy is after administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition. In some embodiments, the radiation therapy is concurrent with administration of the compound of structural Formula (I), or a pharmaceutically acceptable salt thereof or the pharmaceutical composition.

[0034] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0035] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "Figure" and "FIG." herein), of which:

[0037] FIG. 1A-1B. A schematic representation of intra-patient dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics **(A).** A schematic representation of inhibition of CRF_1 with a CRF_1 antagonist (Compound 1) **(B)**.

[0038] FIG. 2. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

[0039] FIG. 3. Graphic representation of pharmacokinetics (dose-proportional, adequate exposure at safe doses) in patients with CAH following 14-days of once daily dosing at each dose level with a CRF_1 antagonist (Compound 1).

[0040] FIG. 4. Graphic representation of patient-level response (measuring ACTH levels) to a CRF_1 antagonist (Compound 1).

[0041] FIG. 5A-5B. Graphic representation of patient-level response of sample responders (measuring ACTH levels) to a CRF_1 antagonist [~~Subject 003001~~Patient 10 **(A)**; ~~Subject 007002~~ Patient 8 **(B)**].

[0042] FIG. 6. Graphic representation of patient-level response (measuring 17-OHP levels) to a CRF_1 antagonist (Compound 1).

[0043] FIG. 7A-7B. Graphic representation of patient-level response of sample responders (measuring 17-OHP levels) to a CRF_1 antagonist [~~Subject 003001~~Patient 10 **(A)**; ~~Subject 007002~~ Patient 8 **(B)**].

[0044] FIG. 8. Graphic representation of patient-level response (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1).

[0045] FIG. 9A-9B. Graphic representation of patient-level response of sample responders (measuring androstenedione levels) to a CRF_1 antagonist (Compound 1) [~~Subject 003001~~Patient 10 **(A)**; ~~Subject 007002~~ Patient 8 **(B)**].

[0046] FIG. 10A-10B. Images of a patient with TART pre-treatment with a CRF_1 antagonist (Compound 1) **(A)** and 6-weeks post-treatment with a CRF_1 antagonist (Compound 1) **(B)**.

[0047] FIG. 11A-11B. Graphic representation of an *in vitro* binding assay of a CRF_1 antagonist (Compound 1); ^{125}I-sauvagine binding to rat cerebellar membranes one hour after oral

administration of increasing Compound 1 doses **(A)** and *in vivo* inhibition of CRF-induced activity after treatment with a CRF_1 antagonist; Compound 1 (oral, 10 mg/kg) **(B)**.

[0048] FIG. 12A-12B. ~~Graphic representation of ACTH levels **(A)** and 17-OHP levels **(B)** after treatment with a CRF_1 antagonist (Compound 1)~~ Graphic representation of ACTH levels (A) and 17-OHP levels (B) after treatment with a CRF_1 antagonist.

[0049] FIG. 13. Graphic representation of hormone responses after treatment with a CRF_1 antagonist (Compound 1).

[0050] FIG. 14 depicts the proof of concept and escalating QD dosing at 10 pm for Cohort A and the single dose level and BID dosing at 10 am and 10 pm for Cohort B.

[0051] FIG. 15A-15D are graphic representations of changes in androstenedione seen in participants in Cohort A and Cohort B.

[0052] FIG. 16A-16D are graphic representations of changes in 17-hydroxyprogesterone seen in participants in Cohort A and Cohort B.

[0053] FIG. 17A-17D are graphic representations of changes in adrenocorticotropic hormone seen in participants in Cohort A and Cohort B.

DETAILED DESCRIPTION

[0054] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

I. Definitions

[0055] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0056] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0057] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl,

isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

[0058] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -$CH_2CH_2CH_2CH_2$-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0059] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: -CH_2-CH_2-O-CH_3, -CH_2-CH_2-NH-CH_3, -CH_2-CH_2-N(CH_3)-CH_3, -CH_2-S-CH_2-CH_3, -CH_2-CH_2, -S(O)-CH_3, -CH_2-CH_2-S(O)$_2$-CH_3, -CH=CH-O-CH_3, -Si(CH_3)$_3$, -CH_2-CH=N-OCH_3, -CH=CH-N(CH_3)-CH_3, -O-CH_3, -O-CH_2-CH_3, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3 and -CH_2-O-Si(CH_3)$_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

[0060] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH_2-CH_2-S-CH_2-CH_2- and -CH_2-S-CH_2-CH_2-NH-CH_2-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and

heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0061] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

[0062] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0063] The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0064] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term

"heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

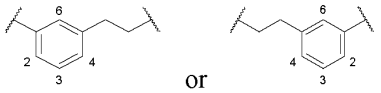
[0065] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted

heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0066] The symbol "〰" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0067] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0068] The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



[0069] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -CHO, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2CH_3$ $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0070] Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0071] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', $-NR''C(O)_2R'$, -NR-C(NR'R''R''')=NR'''', -NR-C(NR'R'')=NR''', $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R''$, $-NRSO_2R'$, –NR'NR''R''', –ONR'R'', –NR'C(O)NR''NR'''R'''', -CN, $-NO_2$, $-NR'SO_2R''$, -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R'', R''', and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g.,

aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0072] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, -SiR'R"R'", -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", $-NR"C(O)_2R'$, -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'", $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, –NR'NR"R'", –ONR'R", –NR'C(O)NR"NR'"R"", -CN, $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R'", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" groups when more than one of these groups is present.

[0073] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent),

the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0074] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0075] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C"R"R"')_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R", and R"' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0076] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0077] A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, -CF_3, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –NHC=(O)$NHNH_2$, –NHC=(O) NH_2, -$NHSO_2H$, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF_3, -$OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

[0078] A "size-limited substituent" or " size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or

unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0079] A "lower substituent" or " lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0080] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0081] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0082] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0083] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0084] As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0085] The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0086] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0087] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0088] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0089] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0090] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0091] "Analog" or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0092] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0093] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R^{13} substituents are present, each R^{13} substituent may be distinguished as R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc., wherein each of R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc. is defined within the scope of the definition of R^{13} and optionally differently.

[0094] A "detectable moiety" as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

[0095] Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0096] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities,

acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0097] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0098] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents. In embodiments, compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present invention.

[0099] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after

administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0100] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0101] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of a compound to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0102] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0103] A "CRF1 inhibitor" refers to a compound (e.g., compounds described herein) that reduces the activity of CRF1 when compared to a control, such as absence of the compound or a compound with known inactivity.

[0104] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally

occurring amino acid polymer. In embodiments, the terms "polypeptide," "peptide," and "protein", used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

[0105] A polypeptide, or a cell is "recombinant" when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, *e.g.*, in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

[0106] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

[0107] The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway (e.g., MAP kinase pathway).

[0108] As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

[0109] The terms "agonist," "activator," "upregulator," etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in

comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist. In embodiments, an agonist is a molecule that interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

[0110] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

[0111] The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. An antagonist prevents, reduces, inhibits, or neutralizes the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An "antagonist" is a molecule that opposes the action(s) of an agonist.

[0112] The terms "corticotropin-releasing factor type-1," "CRF_1," "corticotropin-releasing hormone receptor 1," and "CHHR1" refer to a protein (including homologs, isoforms, and functional fragments thereof) and is a receptor for corticotropin releasing-hormone. The terms

include any recombinant or naturally-occurring form of CRF_1 variants thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF1). The terms include any mutant form of CRF_1 variants (e.g., frameshift mutations) thereof that maintain CRF_1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype CRF_1). In embodiments, the CRF_1 protein encoded by the *CRHR1* gene has the amino acid sequence set forth in or corresponding to Entrez 1233, UniProt P34998.

[0113] The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.*).

[0114] The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a malignant or benign tumor (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)). The disease may be cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, adrenal, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

[0115] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include adrenal cancer and tumors (e.g., testicular adrenal rest tumors (TART) or ovarian adrenal rest tumors (OART)) brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal

carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[0116] The term "congenital adrenal hyperplasia" or "CAH" are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis). These conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children, or adults.

[0117] "Adrenal rest tumor" refers to a neoplasm of the testis (or ovaries) consisting of adrenal tissue. It may be secondary to hyperplasia of an adrenal gland.

[0118] "Testicular adrenal rest tumor(s)" or "TART" and/or ovarian adrenal rest tumor(s) are a complication of congenital adrenal hyperplasia (CAH), which may develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. TART lesions are typically located within the rete testis and are bilateral, synchronous, nodular and multiple. TART can lead to testicular structural damage, spermatogenesis disorders, infertility and mass-forming lesions.

[0119] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal